Search Strategy

Stedman's Medical Dictionary 27th Edition
potentiation: Interaction between two or more drugs or agents resulting in a pharmacologic response greater than the sum of individual responses to each drug or agent.

FILE 'USPATFULL' ENTERED AT 17:31:04 ON 11 DEC 2002

		E	SMITH KENDALL A/IN
L1	12	S	E3
L2	11363	S	(IL-2 OR INTERLEUKIN-2)
L3	5911	S	L2 AND (ANTIVIRAL OR ADJUVANT OR IMMUNE POTENTIAT?)
L4	2265	S	L3 AND ANTIVIRAL?
L5	1521	S	L4 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L6	198	S	L4 AND (IL-2/CLM OR INTERLEUKIN-2/CLM)
L7	107	S	L6 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L8	47	S	L7 AND (HIV/CLM OR HUMAN IMMUNODEFICIENCY VIRUS/CLM)
L9	30	S	L6 AND (HCV OR HEPATITIS C VIRUS)
L10	12	S	L9 AND (HCV/CLM OR HEPATATIS/CLM)

FILE 'MEDLINE' ENTERED AT 18:09:09 ON 11 DEC 2002

		E	SMITH K A/AU
L11	305	S	E3-E5
L12	84	S	L11 AND (IL-2 OR INTERLEUKIN-2)
L13	44911	S	(IL-2 OR INTERLEUKIN-2)
L14	44827	S	L13 NOT L11
L15	673	S	L14 AND (IMMUNE POTENTIATION OR IMMUNOPOTENTATION OR POTENTIA
L16	67	S	L15 AND (VIR?)
L17	221	S	L15 AND (IL-2/TI OR INTERLEUKIN-2/TI)
L18	210	S	L17 NOT L16

FILE 'USPATFULL' ENTERED AT 13:24:56 ON 14 JAN 2004

L1	3419	S	(HCV OR HEPATITIS C VIRUS)
L2	856	S	L1 AND (IL-2 OR INTERLEUKIN-2)
L3	110	S	L2 AND (IL-2/CLM OR INTERLEUKIN-2/CLM)
L4	58	S	L3 AND (HCV/CLM OR HEPATITIS/CLM)
L5	22	S	L4 AND AY<2000
L6	30078	S	(HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L7	8912	S	L6 AND (IL-2 OR INTERLEUKIN-2)
L8	623	S	L7 AND (IL-2/CLM OR INTERLEUKIN-2/CLM)
L9	162	S	L8 AND (HIV/CLM OR HUMAN IMMUONODEFICIENCY VIRUS/CLM)
L10	83	S	L9 AND AY<2000

FILE 'MEDLINE' ENTERED AT 14:08:52 ON 14 JAN 2004

L11	18469	S	(HCV OR HEPATITIS C VIRUS)
L12	142	S	L11 AND (IL-2 OR INTERLEUKIN-2)
L13	26	S	L12 AND (IL-2/TI OR INTERLEUKIN-2/TI)
L14	137517	S	(HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L15	1872	S	L14 AND (IL-2 OR INTERLEUKIN-2)
L16	850	S	L15 AND (THERAP? OR TREAT?)
L17	36	S	L16 AND (LOW-DOSE)

L1 ANSWER 3 OF 12 USPATFULL
2000:40633 Method of stimulation of immune response with low doses of IL-2.
Smith, Kendall A., New York, NY, United States
Cornell Research Foundation, Inc., Ithaca, NY, United States (U.S. corporation)
US 6045788 20000404
APPLICATION: US 1996-608516 19960228 (8)
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A method of activating the immune system of a subject comprises the chronic administration of low doses of an agent such as IL-2, fusion proteins thereof and derivatives thereof that are pharmaceutically acceptable. The agent is provided as a dermal composition, transdermal delivery device and electrotransport device as well as in the form of a kit for self-administration.

CLM What is claimed is:

1. A method of chronic stimulation and/or maintenance of immune response, comprising the administration or application or self-application to a subject or the subject's self-administration of a composition comprising an agent selected from the group consisting of natural and recombinant IL-2, pharmaceutically-acceptable fusion proteins of natural and recombinant IL-2, PEG-natural and -recombinant IL-2, lipid-conjugated natural and recombinant IL-2, therapeutic agent-linked natural and recombinant IL-2, reduced natural and recombinant IL-2, glycosylated natural and recombinant IL-2, non-glycosylated natural and recombinant IL-2, and mixtures thereof, for a period greater than three months in an amount and under conditions effective to release about 100,000 to about 500,000 IU IL2/m.sup.2 body surface/day or equivalent to about 1,000 to about 500,000 IU IL-2/m.sup.2 body surface/day, the agent having a specific activity or 15.times.10.sup.6 IU/mg protein.

2. The method of claim 1, wherein the composition is administered, applied, self-administered, or self-applied by subcutaneous, intramuscular, intradermal, intralymphatic, intratumor, transdermal, intracavitary, transbuccal, transpulmonary, oral, intranasal, transmucosal, intravaginal, intraanal, intrabuccal, or sublingual administration or application, by inhalation, or by implant.

3. The method of claim 1, wherein the composition is self-administered.

4. The method of claim 1, wherein the composition comprises a controlled release composition.

5. The method of claim 1, further comprising adjusting the amount of the agent administered, applied, self-administered, or self-applied by monitoring the blood concentration of the agent, the % saturation of the high affinity IL-2 receptors, or the blood count of at least a cell type selected from the group consisting of circulating lymphocytes, monocytes, and polymorphonuclear leukocytes.

6. The method of claim 1, wherein the subject is a normal subject or a subject afflicted with a condition associated with a viral, bacterial, fungal, and parasitic microorganism, a congenital or acquired immunodeficiency, or a malignancy.

7. The method of claim 6, wherein the subject is HIV seropositive human; and the composition is administered applied, self-administered, or self-applied in an amount and under conditions which substantially avoid increasing the count of circulating microorganisms.

8. The method of claim 1, wherein the subject is an animal.

9. The method of claim 8, wherein the animal is a human.

10. The method of claim 1, wherein the amount of the agent administered, allied, self-administered, or self-applied is effective to elevate the count of at least one blood cell type selected from the group consisting of circulating lymphocytes, monocytes, pa polymorphonuclear leukocytes.

11. The method of claim 10, wherein the amount of the agent administered, applied, self-administered, or self-applied is effective to elevate the count of at least one blond cell selected from the group consisting of circulating T-cells, B-cells, NK cells, monocytes, eosinophils, neutrophils, basophils and antigen-presenting cells.

12. The method of claim 1, wherein the administered, applied, self-administered or self-applied composition is in the form of a powder, a tablet, a capsule, a dragee, a cream, a solution, a suspension, an emulsion, a gel, a spray, a liposome or other micelle, or combinations or mixtures thereof, and formulated prior to administration, application, self-administration or self-application.

13. The method of claim 1, wherein the administered or self-applied composition is in solid form, and formulated prior to administration, application, self-administration, or self-application.

14. The method of claim 13, wherein the administered, applied self-administered or self-applied composition is in lyophilized form.

15. The method of claim 1, wherein the administered, applied, self-administered or self-applied composition is in liquid form.

16. The method of claim 1, wherein the composition is administered, applied, self-administered, or self-applied by means of an inhalant.

17. The method of claim 1, wherein the agent is administered, applied, self-administered, or self-applied as a topical composition, further comprising a carrier or diluent for the agent suitable for topical delivery and an ingredient selected from the group consisting of buffers, salt forming acids and bases, perfumes, colorants, emollients, adjuvants, single or multiple enteric coatings, copolymers, microporous or semi-permeable membranes, enzyme inhibitors, mucoadhesives, chelating agents, particulate systems, viral envelope proteins, liposomes and other micelles, emulsifiers, lipoproteins and other fatty acid derivatives, surfactants, bile salts, hydrophilic, neutral, and hydrophobic polymers and co-polymers, hydrogels, biodegradable polymers and co-polymers, and an additional bioactive agent selected from the group consisting of additional lymphokines or cytokines , and fusion proteins of the lymphokines or cytokines, anti-inflammatories, anti-bacterial, anti-viral, anti-fungal, anti-parasitic, anti-metabolic, anti-inflammatory, vasoactive, anti-neoplastic, bronchodilating, local anesthetic, immunomodulating, growth promoting and regenerating agents, enzymatic, hormonal agents, neurotransmitters, and cell receptor proteins and ligands.

18. The method of claim 17, wherein the composition is in the form of a cream, an ointment, a solution, a gel, a powder, a suspension, an emulsion, encapsulated particles or mixtures thereof.

19. The method of claim 17, wherein the agent is present in an amount of

about 0.0001 to 50 wt % of the composition.

20. The method of claim 17, wherein the composition comprises a controlled release composition.

21. The method of claim 17, wherein the composition is administered by a transdermal delivery device comprising, in a sterile container, a solid support; and a compartment provided in the solid support, the compartment comprising a solution or suspension of the composition, and having one side permeable thereto; whereby when the permeable side of the compartment is placed in contact with an area of a subject's dermis a desired amount of the agent passes from the device onto, and through, the dermis of the subject, over a pre-determined period of time.

22. The method of claim 21, wherein the device comprises a unit dose of the agent.

23. The method of claim 21, wherein the device further comprises a cover placed on the permeable side of the container; the cover being substantially impermeable to the solution or suspension and removable prior to administration, application, or self-application.

24. The method of claim 21, wherein the device is an electrotransport device, further provided with donor and counter electrodes; external power source and control circuitry; wherein the solution or suspension further comprises electroconducting agents, and when the permeable side of the device is placed in contact with an area of the subject's dermis and an electric field is applied to the electrodes, a desired amount of the agent passes from the device onto, and through, the dermis of the subject, over a pre-determined period of time.

25. The method of claim 21, wherein the device is an ultrasound device, further provided with ultrasound transducer, external power source and control circuitry; wherein when the permeable side of the device is placed in contact with an area of the subject's dermis and an electric field is applied to the ultrasound generator, a desired amount of the agent passes from the device onto, and through, the dermis of the subject, over a pre-determined period of time.

26. The method of claim 20, wherein the agent is released by an implant, the implant comprising an amount effective to release the desired amount of the agent over a predetermined period of time.

27. The method of claim 1, further comprising administering or applying to the subject or having the subject self-administer or self-apply a bioactive agent selected from the group consisting of additional lymphokines or cytokines, fusion proteins of the lymphokines or cytokines, anti-inflammatory, anti-bacterial, anti-viral, anti-fungal, anti-parasitic, anti-metabolic, vasoactive, anti-neoplastic, bronchodilating, local anesthetic, immunomodulating, growth promoting, regenerating, enzymatic and hormonal agents, neurotransmitters, and cell receptor proteins and ligands.

28. The method of claim 27, wherein the subject is administered, applied, self-administered, or self-applied the agent and a bioactive agent selected from the group consisting of anti-bacterial agents, anti-fungal agents, anti-parasitic agents and anti-viral agents.

29. The method of claim 28, wherein tie bioactive agent comprises one or more anti-viral agents.

30. The method of claim 29, wherein the anti-viral agents are selected from the group consisting of nucleotide analogues and protease inhibitors.

31. The method of claim 30, wherein the subject is administered, applied, self-administers or self-applies, one or more anti-viral agents selected from the group consisting of zidovudine (AZT), 2',3'-dideoxyinosine (ddI), 3'-azido- 2', 3'-dideoxythymidine, d4T, acyclovir, 1,3-dihydro-2-propoxy-methyquanine (gancyclovir), ribavirin, dideoxycytidine (ddC), lamivudine (3TC), and enzyme inhibitors.

32. The method of claim 31, wherein the subject is administered or applied, self-administers or self-applies one or more enzyme inhibitors, and the enzyme inhibitors comprise protease inhibitors.

33. The method of claim 32, wherein the protease inhibitors are saquinovir or invirase.

34. The method of claim 31, wherein the subject is administered or applied, self-administers or self-applies one or more anti-viral agents, and the anti-viral agents are selected from the group consisting of zidovudine (AZT), lamivudine (3TC), d4T, invirase and combinations and mixtures thereof.

35. The method of claim 34, wherein the anti-vital agent combinations administered, applied, self-administered or self-applied comprise zidovudine (AZT), lamivudine (3TC), and d4T, or zidovudine (AZT), lamivudine (3TC), and invirase.

36. The method of claim 35, wherein the anti-viral agent combination administered, applied, self-administered or self-applied comprises zidovudine (AZT), lamivudine (3TC), and d4T, and zidovudine is administered, applied, self-administered or self-applied at about 600 mg/day, lamivudine (3TC) at about 300 mg/day, and invirase at about 600 mg/day.

37. The method of claim 28, wherein the subject is administered, applied, self-administers or self-applies one or more bioactive agents.

38. The method of claim 37, wherein the bioactive agents comprise anti-bacterial agents.

39. The method of claim 37, wherein the anti-bacterial agents comprise antibiotics.

40. The method of claim 39, wherein the antibiotics are selected from the group consisting of pentamidines, trimethoprim-sulfamethoxazole, sulfonamides, penicillins, cephalosporins, aminoglycosides, tetracyclines, chloramphenicols, and combinations and mixtures thereof.

41. The method of claim 37, wherein the bioactive agents comprise anti-fungal agents.

42. The method of claim 41, wherein the anti-fungal agents are selected from the group consisting of flucytosine, amphotericin B, fluconazole, griseofulvine, and combinations and mixtures thereof.

43. The method of claim 37, wherein the bioactive agents comprise anti-parasitic agents.

44. The method of claim 43, wherein the anti-parasitic agents are

selected from the group consisting of pyrimethamine, quinacrine, thiabendazole, levamisol, and combinations and mixtures thereof.

45. The method of claim 37, wherein the bioactive agents comprise anti-metabolic agents.

46. The method of claim 45, wherein the anti-metabolic agents are selected from the group consisting of purine analogues, folic acid analogues, pyrimidine analogues, and combinations and mixtures thereof.

47. A method of chronic stimulation and/or maintenance of immune response, comprising the administration or application to a subject in need of treatment or the subject's self-administration, or self-application of an agent selected from the group consisting of natural and recombinant IL-2, pharmaceutically-acceptable fusion proteins of natural or recombinant IL-2, PEG-natural and recombinant IL-2, lipid-conjugated natural and recombinant L-2, therapeutic agent-linked natural and recombinant IL-2, reduced natural and recombinant IL-2, glycosylated natural and recombinant IL-2, non-glycosylated natural and recombinant IL-2, and mixtures thereof, for a period greater than three months in an amount and under conditions effective to release about 100,000 to about 500,000 IU IL-2/m.sup.2 body surface/day or equivalent to about 100,000 to about 500,000 IU IL-2/m.sup.2 body surface/day, the agent having a specific activity of 15.times.10.sup.6 IU/mg protein.

48. A method of increasing and/or maintaining the count of circulating blood cells selected from tie group consisting of lymphocytes, monocytes, and polymorphonuclear leukocytes, comprising the administration or application to a subject or the subject's self-administration, or self-application of a composition comprising an agent selected from the group consisting of natural and recombinant IL-2, pharmaceutically acceptable Fusion proteins of natural and recombinant IL-2, PEG-IL-2 natural and recombinant, lipid-conjugated natural and recombinant IL-2, therapeutic agent-linked natural and recombinant IL-2, reduced natural and recombinant IL-2, glycosylated natural and recombinant IL-2, non-glycosylated natural and recombinant IL-2, and mixtures thereof, for a period greater than three months in an amount and under conditions effective to release about 100,000 to about 500,000 IU IL-2/m.sup.2 body surface/day or equivalent to about 100,000 to about 500,000 IU IL-2/m.sup.2 body surface/day, the agent having a specific activity of 15.times.10.sup.6 IU/mg protein.

49. The method of claim 48, wherein the composition further comprises an ingredient selected from the group consisting of carriers, diluents, buffers, salt forming acids and bases, perfumes, colorants, emollients, adjuvants, single or multiple enteric coatings, copolymers, microporous or semi-permeable membranes, enzyme inhibitors, mucoadhesives, chelating agents, particulate systems, viral envelope proteins, liposomes and other micelles, emulsifiers, lipoproteins and other fatty acid derivatives, surfactants, bile salts, hydrophilic, neutral, and hydrophobic polymers and co-polymers, hydrogels, biodegradable polymers and co-polymers, and anti-inflammatories, an additional bioactive agent selected from the group consisting of additional lymphokines or cytokines, and fusion proteins of the lymphokines or cytokines, anti-inflammatories, anti-bacterial, anti-viral, anti-fungal, anti-parasitic, anti-metabolic, anti-inflammatory, vasoactive, anti-neoplastic, bronchodilating, local anesthetic, immunomodulating, growth promoting and regenerating agents, enzymatic, hormonal agents, neurotransmitters, and cell receptor proteins and ligands.

50. The method of claim 48, wherein the subject is selected from the group consisting of normal subjects and subjects afflicted with a condition associated with a viral, bacterial, fungal, and parasitic microorganism, a congenital and acquired immunodeficiency, and a malignancy.

51. The method of claim 50, wherein the subject is an HIV seropositive human, and the agent is administered, applied, self-administered, or self-applied in an amount and under conditions which avoid increasing the count of circulating microorganisms.

52. A method of administering or applying to a subject an agent selected from the group consisting of natural and recombinant IL-2, pharmaceutically acceptable fusion proteins of natural and recombinant IL-2, PEG-IL-2 natural and recombinant, lipid-conjugated natural and recombinant IL-2, therapeutic agent-linked natural and recombinant IL-2, reduced natural and recombinant IL-2, glycosylated natural and recombinant IL-2, non-glycosylated natural and recombinant IU-2, and mixtures thereof in the absence of toxicity grade 1 or higher, comprising the administration, application, self-administration, or self-application for a period greater than three months of a composition comprising the agent in an amount and under conditions effective to release about 100,000 to about 500,000 IU IL-2/m.sup.2 body surface/day or equivalent to about 100,000 to about 500,000 IU IL2/m.sup.2 body surface/day, the agent having a specific activity of 15.times.10.sup.6 IU/mg protein.

53. The method of claim 52, wherein the subject is selected from the group consisting of normal subjects and subjects afflicted with a condition associated with a viral, bacterial, fungal, and parasitic microorganism, a congenital and acquired immunodeficiency, and a malignancy.

54. The method of claim 53, wherein the subject is an HIV seropositive human, and the agent is administered, applied, self-administered, or self-applied in an amount and under conditions which avoid increasing the count of circulating microorganisms.

55. A method of administering or applying to a subject an agent selected from the group consisting of natural and recombinant IL-2, pharmaceutically acceptable fusion proteins of natural and recombinant IL-2, PEG-IL2 natural and recombinant, lipid-conjugated natural and recombinant IL-2, therapeutic agent-linked natural and recombinant IL-2, reduced natural and recombinant IL-2, glycosylated t in a IL-2, non-glycosylated natural and recombinant IL-2, and mixtures thereof, comprising the administration, application, self-administration, or self-application for a period greater than three months of a therapeutic product comprising the agent, which when administered or applied lo a subject releases an amount of the agent over a pre-determined period of time effective to release about 100,000 to about 500,000 IU IL-2/m.sup.2 body surface/day or equivalent to about 100,000 to about 500,000 IU IL-2/m.sup.2 body surface/day, the agent having a specific activity of 15.times.10.sup.6 IU/mg protein.

56. The method of claim 55, wherein the product further comprises an ingredient selected from the group consisting of carriers, diluents, buffers, salt forming acids and bases, perfumes, colorants, emollients, adjuvants, single or multiple enteric coatings, copolymers, microporous or semi-permeable membranes, enzyme inhibitors, mucoadhesives, chelating agents, particulate systems, viral envelope proteins, liposomes and other micelles, emulsifiers, lipoproteins and other fatty acid

derivatives, surfactants, bile salts, hydrophilic, neutral, and hydrophobic polymers and co-polymers, hydrogels, biodegradable polymers and co polymers, and anti-inflammatories, an additional bioactive agent selected from the group consisting of additional lymphokines or cytokines, and fusion proteins of the lymphokines or cytokines, anti-inflammatories, anti-bacterial, anti-viral, anti-fungal, anti-parasitic, anti-metabolic, anti-inflammatory, vasoactive, anti-neoplastic, bronchodilating, local anesthetic, immunomodulating, growth promoting and regenerating agents, enzymatic, hormonal agents, neurotransmitters, and cell receptor proteins and ligands.

57. The method of claim 55, wherein the subject is selected from the group consisting of normal subjects and subjects afflicted with a condition associated with a viral, bacterial, fungal, and parasitic microorganism, a congenital and acquired immunodeficiency, and a malignancy.

58. The method of claim 57, wherein the subject is an HIV seropositive human, and the agent is administered, applied, self-administered, or self-applied in an amount and under conditions which avoid increasing the count of circulating microorganisms .

59. The method of claim 29, wherein the subject is a normal subject or a subject afflicted with a condition associated with a viral, bacterial, fungal, and parasitic microorganism, a congenital or acquire immunodeficiency, or a malignancy.

60. The method of claim 59, wherein the subject is an HIV scropositive human; and the composition is administered, applied, self-administered, or self-applied in an amount and under conditions which substantially avoid increasing the count of circulating microorganisms.

L8 ANSWER 14 OF 47 USPATFULL
2002:92231 Methods of therapy for HIV infection.
Sahner, David, Berkeley, CA, UNITED STATES
US 2002048748 A1 20020425
APPLICATION: US 2001-974470 A1 20011009 (9)
PRIORITY: US 2000-242090P 20001020 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Methods for promoting immunologic control of human immunodeficiency virus (HIV) in an HIV-infected subject are provided. The methods comprise administering to the subject highly active antiretroviral therapy (HAART) for at least one cycle of an intermittent dosing regimen in combination with administration of a pharmaceutical composition comprising a therapeutically effective amount of interleukin-2 (IL-2) or variant thereof. The combination of daily or intermittent administration of IL-2 (or variant thereof) and intermittent HAART promotes immunologic control of viral replication in the absence of HAART, thereby prolonging the length of time a patient may discontinue HAART before viral rebound necessitates further administration of HAART. Administration of IL-2 therapy in combination with an intermittent HAART dosing regimen provides an effective method for treating a subject infected with HIV.

CLM What is claimed is:
1. A method of promoting immunologic control of human immunodeficiency virus (HIV) in an HIV-infected subject, said method comprising administering to said subject highly active antiretroviral therapy (HAART) for at least

one cycle of an intermittent dosing regimen in combination with administration of a pharmaceutical composition comprising a therapeutically effective amount of interleukin-2 (IL-2) or variant thereof, wherein said administration provides a baseline level of said IL-2 within said subject.

2. The method of claim 1, wherein said HAART comprises daily administration of at least three antiretroviral agents, wherein a therapeutically effective amount of each of said antiretroviral agents is administered.

3. The method of claim 2, wherein said antiretroviral agents are selected from the group consisting of reverse transcriptase inhibitors and protease inhibitors.

4. The method of claim 3, wherein said reverse transcriptase inhibitors are selected from the group consisting of dideoxyinosine (ddI), zidovudine (AZT), zalcitabine (ddC), lamivudine (3TC), stavudine (D4T), abacavir, delavirdine, efavirenz, and nevirapine.

5. The method of claim 3, wherein said protease inhibitors are selected from the group consisting of Indinavir (IDV), Amprenavir, saquinavir, ritonavir, ABT-378, nelfinavir, and GW141.

6. The method of claim 1, wherein said intermittent dosing regimen for HAART comprises administering HAART to said subject until plasma viral RNA is undetectable in said subject, and then discontinuing administration of said HAART until plasma viral RNA reaches an acceptable threshold level in said subject.

7. The method of claim 6, wherein said plasma viral RNA is undetectable in said subject for at least about one month prior to discontinuing HAART, and wherein said acceptable threshold level of said plasma viral RNA is about 10,000 molecules/ml at two consecutive measurements taken about one week apart.

8. The method of claim 1, wherein said IL-2 or variant thereof is administered subcutaneously.

9. The method of claim 1, wherein said IL-2 or variant thereof is administered daily.

10. The method of claim 9, wherein said therapeutically effective amount of said IL-2 or variant thereof is in the range from about 0.6 mIU/M.sup.2 to about 3.5 mIU/m.sup.2.

11. The method of claim 10, wherein said therapeutically effective amount of said IL-2 or variant thereof is in the range from about 0.7 mIU/m.sup.2 to about 3 mIU/m.sup.2

12. The method of claim 11, wherein said therapeutically effective amount of said IL-2 or variant thereof is about 1.20 mIU/m.sup.2.

13. The method of claim 1, wherein said IL-2 or variant thereof is administered intermittently.

14. The method of claim 1, wherein said pharmaceutical composition comprising IL-2 or variant thereof is selected from the group consisting of a stabilized monomeric IL-2

pharmaceutical composition, a multimeric IL-2 composition, a stabilized lyophilized IL-2 pharmaceutical composition, and a stabilized spray-dried IL-2 pharmaceutical composition.

15. The method of claim 14, wherein said IL-2 is recombinantly produced IL-2 having an amino acid sequence for human IL-2 or variant thereof.

16. The method of claim 15, wherein said variant thereof has an amino acid sequence having at least about 70% sequence identity to the amino acid sequence for said human IL-2.

17. A method of treating a subject infected with human immunodeficiency virus (HIV), said method comprising administering to said subject highly active antiretroviral therapy (HAART) for at least one cycle of an intermittent dosing regimen in combination with administration of a pharmaceutical composition comprising a therapeutically effective amount of interleukin-2 (IL-2) or variant thereof, wherein said administration provides a baseline level of said IL-2 within said subject.

18. The method of claim 17, wherein said HAART comprises daily administration of at least three antiretroviral agents, wherein a therapeutically effective amount of each of said antiretroviral agents is administered.

19. The method of claim 18, wherein said antiretroviral agents are selected from the group consisting of reverse transcriptase inhibitors and protease inhibitors.

20. The method of claim 19, wherein said reverse transcriptase inhibitors are selected from the group consisting of dideoxyinosine (ddI), zidovudine (AZT), zalcitabine (ddC), lamivudine (3TC), stavudine (D4T), abacavir, delavirdine, efavirenz, and nevirapine.

21. The method of claim 19, wherein said protease inhibitors are selected from the group consisting of Indinavir (IDV), Amprenavir, saquinavir, ritonavir, ABT-378, nelfinavir, and GW141.

22. The method of claim 17, wherein said intermittent dosing regimen for HAART comprises administering HAART to said subject until plasma viral RNA is undetectable in said subject, and then discontinuing administration of said HAART until plasma viral RNA reaches an acceptable threshold level in said subject.

23. The method of claim 22, wherein said plasma viral RNA is undetectable in said subject for at least about one month prior to discontinuing HAART, and wherein said acceptable threshold level of said plasma viral RNA is about 10,000 molecules/ml at two consecutive measurements taken about one week apart.

24. The method of claim 17, wherein said IL-2 or variant thereof is administered subcutaneously.

25. The method of claim 17, wherein said IL-2 or variant thereof is administered daily.

26. The method of claim 25, wherein said therapeutically effective amount of said IL-2 or variant thereof is in the

range from about 0.6 mIU/m.sup.2 to about 3.5 mIU/m.sup.2.

27. The method of claim 26, wherein said therapeutically effective amount of IL-2 or variant thereof is in the range from about 0.7 mIU/m.sup.2 to about 3 mIU/m.sup.2.

28. The method of claim 27, wherein said therapeutically effective amount of said IL-2 or variant thereof is about 1.20 mIU/m.sup.2.

29. The method of claim 17, wherein said IL-2 or variant thereof is administered intermittently.

30. The method of claim 17 wherein said pharmaceutical composition comprising IL-2 or variant thereof is selected from the group consisting of a stabilized monomeric IL-2 pharmaceutical composition, a multimeric IL-2 composition, a stabilized lyophilized IL-2 pharmaceutical composition, and a stabilized spray-dried IL-2 pharmaceutical composition.

31. The method of claim 30, wherein said IL-2 is recombinantly produced IL-2 having an amino acid sequence for human IL-2 or variant thereof.

32. The method of claim 31, wherein said variant thereof has an amino acid sequence having at least about 70% sequence identity to the amino acid sequence for said human IL-2.

33. A method of treating a subject infected with human immunodeficiency virus (HIV), said method comprising administering to said subject highly active antiretroviral therapy (HAART) for at least one cycle of an intermittent dosing regimen in combination with interleukin-2 (IL-2) therapy, wherein said IL-2 therapy comprises administering a pharmaceutical composition comprising a therapeutically effective amount of IL-2 or variant thereof throughout each cycle of said intermittent dosing regimen of HAART, wherein said administration provides a baseline level of said IL-2 within said subject, and wherein said intermittent dosing regimen for HAART comprises administering HAART to said subject until plasma viral RNA is undetectable in said subject for at least about one month prior to discontinuing HAART, and then discontinuing administration of said HAART until plasma viral RNA reaches at least about 10,000 molecules/ml at two consecutive measurements taken about one week apart.

34. The method of claim 33, wherein said IL-2 or variant thereof is administered daily by subcutaneous injection.

35. The method of claim 34, wherein said therapeutically effective amount of said IL-2 or variant thereof is in the range from about 0.2 mIU/m.sup.2 to about 5 mIU/m.sup.2.

36. The method of claim 35, wherein said therapeutically effective amount of IL-2 or variant thereof is in the range from about 0.5 mIU/m.sup.2 to about 2 mIU/m.sup.2.

37. The method of claim 36, wherein said therapeutically effective amount of said IL-2 or variant thereof is about 1.20 mIU/m.sup.2.

L8 ANSWER 22 OF 47 USPATFULL
2001:25423 Immunologic enhancement with intermittent interleukin-2 therapy.
Lane, H. Clifford, Bethesda, MD, United States
Kovacs, Joseph A., Potomac, MD, United States
Fauci, Anthony S., Washington, DC, United States
The United States of America as represented by the Department of Health and Human Services, Washington, DC, United States (U.S. corporation)
US **6190656** B1 20010220
APPLICATION: US 1997-922218 19970902 (8)
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A method for activating a mammalian immune system entails a series of IL-2 administrations that are effected intermittently over an extended period. Each administration of IL-2 is sufficient to allow spontaneous DNA synthesis in peripheral blood or lymph node cells of the patient to increase and peak, and each subsequent administration follows the preceding administration in the series by a period of time that is sufficient to allow IL-2 receptor expression in peripheral or lymph node blood of the patient to increase, peak and then decrease to 50% of peak value. This intermittent IL-2 therapy can be combined with another therapy which targets a specific disease state, such as an anti-retroviral therapy comprising, for example, the administration of AZT, ddI or interferon alpha. In addition, IL-2 administration can be employed to facilitate in situ transduction of T cells in the context of gene therapy. By this approach the cells are first activated in vivo via the aforementioned IL-2 therapy, and transduction then is effected by delivering a genetically engineered retroviral vector directly to the patient.

CLM What is claimed is:
1. A method for administration of interleukin-2 (IL-2) to increase immune function in a human subject, comprising: (a) administering an amount of IL-2 to a human subject in a first administration in an amount that is sufficient to increase the CD4 count in the subject as compared with the count prior to IL-2 administration, wherein the administration of IL-2 is continuous over a period of time that is sufficient to allow spontaneous DNA synthesis in peripheral blood or lymph node cells of the subject to increase and peak; (b) measuring the DNA synthesis in cells obtained from the subject during the administration period, wherein a time period of an increase or peak in DNA synthesis is indicative of an optimal duration of interleukin-2 (IL-2) administration; (c) administering a subsequent amount of IL-2 to the subject that is sufficient to increase the CD4 count in the subject as compared to the count prior to IL-2 administration, wherein the subsequent administration of IL-2 is continuous over a period of time that is sufficient to allow spontaneous DNA synthesis in peripheral blood or lymph node cells of the subject to increase and peak, and wherein the subsequent administration of IL-2 follows the first administration of IL-2 by a period of time that is sufficient to allow IL-2 receptor expression in peripheral blood or lymph node cells of the subject to increase as compared to the level of expression prior to IL-2 administration, peak then decrease to 50% of peak value; and (d) measuring the DNA synthesis in cells obtained from the subject during the subsequent administration, wherein a time period of an increase or

peak in DNA synthesis is indicative of an optimal duration of IL -2 administration; and (e) discontinuing administration of the subsequent amount of L2 administration at about the time of peak in DNA synthesis.

2. The method of claim 1, wherein IL-2 is administered in the first administration for a period of time from about one day to about 14 days and the subsequent administration of IL -2 begins at least 4 weeks after the end of the first administration of IL-2.

3. The method of claim 2, wherein the IL-2 is administered for about 5 days.

4. The method of claim 1, wherein the IL-2 is administered at a dosage of from 1.8 to 24 MU/day.

5. The method of claim 1, wherein the subject is an HIV -infected subject.

6. The method of claim 1, wherein the IL-2 administration is effected by continuous infusion.

7. The method of claim 1, wherein the IL-2 administration is effected by a series of subcutaneous injections.

8. The method of claim 7, wherein the IL-2 administration is effected by from 1-3 subcutaneous injections per day.

9. The method of claim 1, wherein IL-2 is administered for a period of time from about one day to about 14 days.

10. A method of activating the immune system of a subject, comprising: administering to the subject an amount of IL-2 sufficient to increase a level of helper/inducer T-cell function in the subject, wherein the IL-2 is administered in a series of successive continuous administrations, wherein each of the continuous administrations extend over a period of from 1 day to 2 weeks, and successive administrations are separated by a period of time of at least 4 weeks, wherein a duration of the continuous infusion is determined by measuring an increase in lymphocyte formation, and discontinuing administration of the IL-2 after a peak of lymphocyte formation has been detected.

11. The method of claim 10, wherein the peak of lymphocyte formation is determined by measuring lymphocyte blast formation.

12. The method of claim 10, wherein the peak of lymphocyte formation is determined by measuring DNA synthesis.

13. The method of claim 10, wherein the subject is infected with the human immunodeficiency virus.

14. A method of stimulating an immune response in a subject, comprising; administering to the subject a therapeutically sufficient dose of IL-2 for a sufficient period of time to stimulate an increase in a CD4 count of the subject compared to prior to administration of the IL-2, wherein the sufficient period of time is determined by identifying peak activation of the immune system by evaluating a parameter of T cell proliferation, and discontinuing administration of the IL-2 when or

after it is determined that peak activation has already occurred.

15. The method of claim 14, wherein peak activation of the immune system is determined by measuring lymphocyte blast formation.

16. The method of claim 15, wherein peak activation of the immune system is determined by measuring DNA synthesis in peripheral blood or lymph node cells of the subject.

17. The method of claim 14, further comprising repeatedly administering the therapeutically sufficient dose of IL-2 to the subject after a sufficient period of time for the subject's immune system to pass through a refractory period of relative resistance to stimulation with IL2.

18. The method of claim 17, further comprising determining that the subject's immune system has passed through the refractory period by determining that IL-2 receptor expression in peripheral blood or lymph node cells of the subject have decreased at least 50% from a peak value of IL-2 receptor expression during IL-2 administration.

L6 ANSWER 189 OF 198 USPATFULL
89:90683 Treatment of infections with lymphokines.
Chong, Kong-Teck, Union City, CA, United States
Cetus Corporation, Emeryville, CA, United States (U.S. corporation)
US 4879111 19891107
APPLICATION: US 1986-853122 19860417 (6)
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Infections in mammalian hosts may be treated therapeutically or prophylactically with an effective amount of at least one lymphokine before or after host infection, the amount being sufficient to achieve at least 50% protection of the host. Preferably, the lymphokine is IL-2 or a combination of TNF and IL-2 or TNF and IFN-.gamma.. Also, preferably the infection is bacterial and is being treated prophylactically. The combination of TNF and IL-2 or TNF and IFN-.gamma. is administered in synergistically effective amounts.
CLM What is claimed is:
1. A method for prophylactic or therapeutic treatment of bacterial infections in mammalian hosts comprising administering an effective amount of tumor necrosis factor (TNF) from a mammalian species, to the host, before or after infection of the host, wherein the amount of TNF is a sufficient dose to achieve at least 50% protection of the host.

2. The method of claim 1 wherein the TNF is from a human source.

3. The method of claim 2 wherein the TNF is recombinant and the treatment is prophylactic.

4. The method of claim 3 wherein the TNF is microbially produced.

5. The method of claim 4 wherein the TNF has its first eight amino acid residues deleted.

6. The method of claim 1 wherein the amount of TNF is a sufficient dose to achieve at least 70% protection of the host.

7. The method of claim 1 wherein the bacterial infection is a Gram-negative infection.

8. The method of claim 1 wherein the TNF is in admixture with a pharmaceutically acceptable carrier medium prior to administration.

9. A method for prophylactic or therapeutic treatment of bacterial infections in mammalian hosts comprising administering an effective amount of tumor necrosis factor (TNF) and interleukin-2 (IL-2), both from a mammalian species, to the host, before or after infection of the host, wherein the amount of TNF and IL-2 is a sufficient dose to achieve at least 50% protection of the host.

10. The method of claim 9 wherein the IL-2 and TNF are from a human source, the amount of IL-2 employed is 15,000-30,000 units and the amount of TNF employed is 0.01-0.02 micrograms per ml.

11. A method for propylactic or therapeutic treatment of bacterial infections in mammalian hosts comprising administering an effective amount of tumor necrosis factor (TNF) and interferon-gamma (IFN-.gamma.), both from a mammalian species, to the host, before or after infection of the host, wherein the amount of TNF and IFN-.gamma. is a sufficient dose to achieve at least 50% protection of the host.

12. The method of claim 11 wherein the TNF and IFN-.gamma. are from a human source.

13. A method for prophylactic or therapeutic treatment of bacterial infections in human host comprising administering an effective amount of recombinant microbial produced human TNF to said host before or after the infection, wherein said amount of TNF is a sufficient dose to achieve at least 50% protection of said host.

14. A method for prophylactic or therapeutic treatment of gram negative bacterial infections in human host comprising administering an effective amount of recombinant microbial produced human TNF to said host before or after the infection, wherein said amount of TNF is a sufficient dose to achieve at least 50% protection of said host.

15. The method of claim 13, wherein said TNF is a mutein of TNF that lacks the first eight amino acids at the amino terminal end.

16. The method of claim 14, wherein said TNF is a mutein of TNF that lacks the first eight amino acids at the amino terminal end.

L12 ANSWER 39 OF 84 MEDLINE
90193650 Document Number: 90193650. PubMed ID: 2315671.
Interleukin-2. Smith K A. (Darmouth Medical
School.) SCIENTIFIC AMERICAN, (1990 Mar) 262 (3) 50-7. Journal code:
0404400. ISSN: 0036-8733. Pub. country: United States. Language: English.

L12 ANSWER 42 OF 84 MEDLINE
89369767 Document Number: 89369767. PubMed ID: 2672465.
Interleukin 2: prototype for a new generation of
immunoactive pharmaceuticals. Ciardelli T; Smith K A. TRENDS IN
PHARMACOLOGICAL SCIENCES, (1989 Jun) 10 (6) 239-43. Ref: 20. Journal
code: 7906158. ISSN: 0165-6147. Pub. country: ENGLAND: United Kingdom.
Language: English.
AB Molecular biological techniques have revealed the interleukin-
2 receptor to be a dimer composed of one alpha-subunit and one
beta-subunit which interact noncovalently in a cooperative manner.
Site-directed mutagenesis, in conjunction with structural analysis, is
beginning to clarify the relationship between structural components of the
receptor and their function, and Thomas Ciardelli and Kendall Smith
explain why this is bringing drug developers closer to the design of
IL-2 agonists and antagonists.

L12 ANSWER 28 OF 84 MEDLINE
92287427 Document Number: 92287427. PubMed ID: 1368227. Rational
immunotherapy with interleukin 2. Kaplan G; Cohn Z A;
Smith K A. (Laboratory of Cellular Physiology & Immunology,
Rockefeller University, New York, NY 10021.) BIO/TECHNOLOGY, (1992 Feb)
10 (2) 157-62. Ref: 44. Journal code: 8309273. ISSN: 0733-222X. Pub.
country: United States. Language: English.
AB Interleukin 2 (IL-2), a T
lymphocyte product released upon antigen stimulation, has been used for
cancer therapy in high doses for more than five years. More recently, its
potential as a stimulant of cell-mediated immunity in infectious diseases,
particularly those caused by intracellular microbes, has become
appreciated. Drawing on the extensive information available as to the
structure, cellular and molecular effects of IL-2,
this review focuses on its use in patients with lepromatous leprosy and
AIDS in low, physiologic doses. The data indicate that IL-
2 is effective in stimulating cell-mediated immunity without
systemic toxicity.

L12 ANSWER 24 OF 84 MEDLINE
93147738 Document Number: 93147738. PubMed ID: 8093894. Prolonged
immunostimulatory effect of low-dose polyethylene glycol
interleukin 2 in patients with human immunodeficiency
virus type 1 infection. Teppler H; Kaplan G; Smith K A; Montana
A L; Meyn P; Cohn Z A. (Laboratory of Cellular Physiology and Immunology,
Rockefeller University, New York, New York 10021.) JOURNAL OF
EXPERIMENTAL MEDICINE, (1993 Feb 1) 177 (2) 483-92. Journal code:
2985109R. ISSN: 0022-1007. Pub. country: United States. Language: English.
AB 13 patients with human immunodeficiency virus type 1 infection class
II-IV, but without opportunistic infection or neoplasm, received 6
micrograms (3.6 x 10(4) IU) of polyethylene glycol recombinant human
interleukin 2 (PEG IL-2)
intradermally twice a week for 4 mo were then followed for an additional 6
mo. Clinical, immunological, and viral parameters were monitored in the
patients, all of whom were taking zidovudine. The cutaneous administration
of PEG IL-2 resulted in an indurated zone resembling a
delayed-type hypersensitivity response of 26 +/- 1 mm diameter (676 mm2)
at 72-96 h after injection throughout the 4 mo of administration. This

dose, which was appreciably lower than in most previous trials, was not associated with local or systemic toxicity. No increase in the viral burden of circulating leukocytes or plasma occurred. A number of immunological functions were stimulated by this course of therapy. All patients demonstrated high levels of lymphokine-activated killer cell activity by cells freshly removed from the circulation and in the absence of in vitro exposure to IL-2. Natural killer cell activity was also enhanced. Limiting dilution analysis revealed an increase in the frequency of IL-2-responsive cells from abnormally low to levels above normal during the course of injections. In a subgroup of four patients with > or = 400 CD4+ T cells/microliter at entry, there was a trend to sustained increases in CD4+ T cell numbers. However, this increase did not reach statistical significance. This subset of patients also exhibited higher proliferative responses to phytohemagglutinin as mitogen. Several of these effects persisted for 3-6 mo after cessation of therapy. In conclusion, low-dose IL-2 regimens lead to sustained immune enhancement in the absence of toxicity. We suggest pursuit of this approach for further clinical trials both as prophylaxis and therapy.

L12 ANSWER 14 OF 84 MEDLINE
96413659 Document Number: 96413659. PubMed ID: 8816813. Rational interleukin 2 therapy for HIV positive individuals: daily low doses enhance immune function without toxicity. Jacobson E L; Pilaro F; Smith K A. (Department of Medicine, New York Hospital-Cornell Medical Center, NY 10021, USA.) PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1996 Sep 17) 93 (19) 10405-10. Journal code: 7505876. ISSN: 0027-8424. Pub. country: United States. Language: English.

AB When administered in high doses to HIV positive (HIV+) individuals, interleukin 2 (IL-2) causes extreme toxicity and markedly increases plasma HIV levels. Integration of the information from the structure-activity relationships of the IL-2 receptor interaction, the cellular distribution of the different classes of IL-2 receptors, and the pharmacokinetics of IL-2 provides for the rationale that low IL-2 doses should circumvent toxicity. Therefore, to identify a nontoxic, but effective and safe IL-2 treatment regimen that does not stimulate viral replication, doses of IL-2 from 62,500 to 250,000 IU/m2/day were administered subcutaneously for 6 months to 16 HIV+ individuals with 200-500 CD4+ T cells/mm3. IL-2 was already detectable in the plasma of most HIV+ individuals even before therapy. Peak plasma IL-2 levels were near saturating for high affinity IL-2 receptors in 10 individuals who received the maximum nontoxic dose, which ranged from 187,500 to 250,000 IU/m2/day. During the 6 months of treatment at this dose range, plasma levels of proinflammatory cytokines remained undetectable, and plasma HIV RNA levels did not change significantly. However, delayed type hypersensitivity responses to common recall antigens were markedly augmented, and there were IL-2 dose-dependent increases in circulating Natural Killer cells, eosinophils, monocytes, and CD4+ T cells. Expanded clinical trials of low dose IL-2 are now warranted, especially in combination with effective antivirals to test for the prevention of immunodeficiency and the emergence of drug-resistant mutants and for the eradication of residual virions.

L12 ANSWER 23 OF 84 MEDLINE
93200498 Document Number: 93200498. PubMed ID: 8453090. Lowest dose interleukin-2 immunotherapy. Smith K A. (Department of Medicine, Dartmouth Medical School, Hanover, NH 03755-3833.

) BLOOD, (1993 Mar 15) 81 (6) 1414-23. Ref: 106. Journal code: 7603509. ISSN: 0006-4971. Pub. country: United States. Language: English.

L12 ANSWER 5 OF 84 MEDLINE
2001283427 Document Number: 20700681. PubMed ID: 11366819. IL-2 low dose and treatment interruption: interview with Kendall A. Smith. Interview by John S. James. Smith K A. AIDS TREATMENT NEWS, (1999 Oct 15) (No 329) 1-6. Journal code: 8809835. ISSN: 1052-4207. Pub. country: United States. Language: English.
AB In an interview, Kendall A. Smith, M.D., whose laboratory identified the IL-2 molecule and the IL-2 receptor, discusses a current study on administering low, daily doses of IL-2 to HIV patients who are also on HAART. One purpose of the study is to see if IL-2 increases the recovery of CD4 cells over an extended period. The second purpose is to see if a patient's immune system might be able to control the virus when HAART is interrupted, but IL-2 treatment is continued. The study results are described. Dr. Smith also discusses the history of IL-2 and other trials currently studying IL-2.

L12 ANSWER 10 OF 84 MEDLINE
1998118735 Document Number: 98118735. PubMed ID: 9457409. Rational interleukin-2 therapy. Smith K A. (Immunology Program, Graduate School of Medical Sciences, Cornell University, USA.) CANCER JOURNAL FROM SCIENTIFIC AMERICAN, (1997 Dec) 3 Suppl 1 S137-40. Journal code: 9513568. ISSN: 1081-4442. Pub. country: United States. Language: English.
AB The administration of cytokines that augment the function of the immune system can be accomplished safely and without toxicity, provided a rational approach is used. Such a therapeutic method should be based upon the principles of pharmacology and the structure-activity relationships of the cytokine-receptor interaction. Thus, the therapeutic index should be determined, and the goal should be to augment the function of the immune system in a variety of clinical situations, not necessarily focused on eradicating a particular disease process such as metastatic cancer that may or may not be influenced by the immune system.

L12 ANSWER 11 OF 84 MEDLINE
97244549 Document Number: 97244549. PubMed ID: 9121530. Interleukin-2 infusions in HIV-infected patients. Jacobson E L; Pilaro F; Smith K A. NEW ENGLAND JOURNAL OF MEDICINE, (1997 Apr 24) 336 (17) 1260-1. Journal code: 0255562. ISSN: 0028-4793. Pub. country: United States. Language: English.

L12 ANSWER 4 OF 84 MEDLINE
2001363436 Document Number: 21317671. PubMed ID: 11424974. Low-dose daily interleukin-2 immunotherapy: accelerating immune restoration and expanding HIV-specific T-cell immunity without toxicity. Smith K A. (Division of Immunology, Weill Medical College of Cornell University, New York, New York 10021, USA.. kasmith@med.cornell.edu) . AIDS, (2001 Feb) 15 Suppl 2 S28-35. Ref: 49. Journal code: 8710219. ISSN: 0269-9370. Pub. country: England: United Kingdom. Language: English.
AB There is now a great deal of interest in therapies focused on improving the function of the immune system in the treatment of individuals infected with the HIV. Although the antiviral drugs effectively suppress replication of the virus, they cannot cure the infection. Therefore, it now appears that both antivirals and immune system stimulants will be necessary to maximally suppress residual latent virus, thereby allowing the discontinuation of the antivirals without relapse of detectable plasma

virus. Interleukin-2 (IL-2) the first cytokine to be discovered at the molecular level has been used as a therapeutic in HIV infection, because it is critical for a normal functioning immune response. IL-2 is essential for the survival and proliferative expansion of antigen-activated T cells and natural killer (NK) cells, and also for promoting their differentiated functions of cytokine secretion and cytolysis. However, as IL-2 stimulates both the innate and acquired immune responses, when used as a therapeutic it can lead to severe toxicity when given in high doses. This review focuses on low dose, daily IL-2 therapy, used to accelerate the recovery of the immune system when viral replication is suppressed maximally with antivirals. In addition, the principles of the use of IL-2 to activate HIV-specific immune reactivity are discussed. At least two signals are required to promote the proliferative expansion and function of antiviral effector lymphocytes, HIV antigens and IL-2.

L12 ANSWER 3 OF 84 MEDLINE

2001543698 Document Number: 21474074. PubMed ID: 11590500. Low-dose daily subcutaneous interleukin-2 in combination with highly active antiretroviral therapy in HIV+ patients: a randomized controlled trial. Lalezari J P; Beal J A; Ruane P J; Cohen C J; Jacobson E L; Sundin D; Leong W P; Raffanti S P; Wheeler D A; Anderson R D; Keiser P; Schrader S R; Goodgame J C; Steinhart C R; Murphy R L; Wolin M J; Smith K A . (Quest Clinical Research, San Francisco, CA, USA.) HIV Clin Trials, (2000 Nov-Dec) 1 (3) 1-15. Journal code: 100936377. ISSN: 1528-4336. Pub. country: United States. Language: English.

AB PURPOSE: Previous studies with intermittent interleukin-2 (IL-2) therapy using intermediate and high levels of IL-2 have demonstrated significant increases in the CD4 + T cell count in HIV-infected patients. Intermittent regimens are amenable to outpatient use, but severe adverse events are frequently experienced with intermediate- and high-dose levels of IL-2. Therefore in this study, the effect of daily, subcutaneous low-dose IL-2 therapy on safety and immunological endpoints was investigated to determine whether immunological benefit could be achieved without toxicity in HIV-infected patients also receiving highly active antiretroviral therapy (HAART). METHOD: A total of 115 patients were enrolled in the trial. Fifty-six asymptomatic HIV-infected patients who had CD4 + T cell counts less than 300 cells/microL at screening and a stable HIV viral load received low-dose IL-2 (1.2 million IU [MIU]/m 2 beginning dose) once daily in conjunction with HAART (IL-2 group). Fifty-nine patients received HAART alone (control group). RESULTS: A dramatic effect of IL-2 on the natural killer (NK) cell population was observed with mean increases of 156 cells/microL in the IL-2 group compared to 19.93 cells/microL in the control group ($p < .001$). Additionally, IL-2-treated patients experienced a statistically significant increase in the mean percentage of CD4 + T cells (3.52% increase) when compared to control patients (1.33% increase) ($p < .001$). The expanded CD4 + T cell population was primarily of the naive phenotype, with mean increases of 4.53% for the IL-2 group and 0.31% for the control group ($p < .001$ for between-group difference). In addition, a higher proportion of IL-2 -treated patients (67%) compared to control patients (33%) achieved increases of greater than 50% in the CD4+ T cell count ($p = .08$). Adverse events of grade 3 or grade 4 toxicity were infrequent in the current study and were substantially lower by comparison to those in studies of intermittent dose IL-2 therapy. Also, negligible changes in the HIV viral load from baseline to final measurement were observed in both groups. A trend toward a reduced number of modifications

of antiretroviral therapy was apparent in the IL-2 group when compared to control patients. CONCLUSION: Daily, low-dose subcutaneous IL-2 therapy in conjunction with HAART is safe and well tolerated and is effective in expanding lymphocyte cell types including NK cells and naive T cells in individuals who have <300 CD4+ T cells.

L12 ANSWER 2 OF 84 MEDLINE

2001543700 Document Number: 21474075. PubMed ID: 11590501. In vivo assessment of antiviral reactivity in chronic HIV infection. Smith K A; Jacobson E L; Sohn T; Warren D; Emert R; Giordano M. (Division of Immunology, Department of Medicine, Weill Medical College, Cornell University, New York 10021, USA.) HIV Clin Trials, (2000 Nov-Dec) 1 (3) 16-22. Journal code: 100936377. ISSN: 1528-4336. Pub. country: United States. Language: English.

AB PURPOSE AND METHOD: Chronic infection with HIV renders individuals incapable of mounting an effective host antiviral response, as defined by in vitro assays. Therefore, to determine whether antiviral reactivity could be detected in vivo, we interrupted effective antiviral treatment prospectively in nine chronically infected aviremic individuals. Low-dose interleukin-2 (IL-2) was administered before and after treatment interruption to compensate for any potential IL-2 production deficiency. In vivo antiviral reactivity was monitored subsequent to the interruption of antiviral therapy via viral and lymphocyte dynamics. The study was terminated when the plasma HIV RNA concentration reached a plateau, defined as four successive determinations that were <25% from the mean. RESULTS: Plasma viral relapse occurred in all participants; reaching a peak concentration within 2.5 weeks. However, over the subsequent 2 weeks viremia was reduced an order of magnitude coincident with a 2-fold lymphocytosis of the CD8 + T cell subset. A second treatment interruption resulted in attenuation of the peak and trough virus concentrations by <10-fold in 3 of 4 participants, while the CD8 + T cell concentrations remained elevated. CONCLUSION: These findings indicate that chronic HIV infection prior to successful antiviral therapy does not preclude host antiviral reactivity. In addition, in vivo antiviral reactivity as revealed by viral and lymphocyte dynamics after antiviral treatment interruption can be useful to monitor the efficacy of different therapies.

L12 ANSWER 1 OF 84 MEDLINE

2002004970 Document Number: 20535320. PubMed ID: 11082734. Restoration of immunity with interleukin-2 therapy. Smith K A ; Jacobson E L; Emert R; Giordano M; Kovacs E; Mumneh N; Pilaro F; Sohn T; Warren D. (Department of Medicine, Weill Medical College of Cornell University, New York, USA.) AIDS Read, (1999 Nov) 9 (8) 563-72. Ref: 64. Journal code: 9206753. ISSN: 1053-0894. Pub. country: United States. Language: English.

AB HIV replication can now be effectively suppressed using antiretroviral combination regimens. The search continues, however, for ways to restore the immune response and eliminate reservoirs of latent infection. Interleukin-2 (IL-2) may augment the immune response in HIV-infected persons. This article discusses the rationale for using IL-2 in those with HIV disease and reviews key trials of IL-2 treatment regimens.

L16 ANSWER 53 OF 67 MEDLINE

92330828 Document Number: 92330828. PubMed ID: 1628132. Cytokine-induced resistance to microbial infections in normal, immunosuppressed and bone marrow transplanted mice. Leshem B; Dekel R; Bercovier H; Tchakirov R; Polacheck I; Zakay-Rones Z; Schlesinger M; Kedar E. (Lautenberg Center for General and Tumor Immunology, Hebrew University-Hadassah Medical School,

Jerusalem, Israel.) BONE MARROW TRANSPLANTATION, (1992 Jun) 9 (6) 471-7. Journal code: 8702459. ISSN: 0268-3369. Pub. country: ENGLAND: United Kingdom. Language: English.

AB We studied the efficacy of in vivo and in vitro treatments with IL-1, IL-2, IL-3, and GM-CSF in the protection against bacterial (Salmonella typhimurium), fungal (Candida albicans) and viral (influenza virus A/PR8) infections, of normal, sublethally irradiated and lethally irradiated, bone marrow (BM) reconstituted mice. In parallel, the cytokines were tested for their ability to potentiate hematopoietic activity in vitro and in vivo. We demonstrate that, under the experimental conditions employed, IL-1 had the best protective activity against the three micro-organisms in both normal and immunocompromised mice when administered in vivo. Administration of IL-2 led to increased resistance in normal but not in immunodeficient mice, whereas GM-CSF had no beneficial effects. In contrast, preincubation of BM cells in these cytokines, singly or combined, prior to transplantation to lethally irradiated mice, did not confer protection against subsequent infection, although it increased the number of BM derived CFU-GM in culture (except in the case of IL -2). Administration of IL-1 or GM-CSF to BM transplanted mice facilitated WBC recovery, whereas IL-2 delayed it. Collectively, the data suggest that IL-1, alone or combined with other cytokines, may be beneficial in the prevention or treatment of microbial infections in immunocompromised and BM transplanted patients. It can also be concluded that enhanced hematopoietic recovery may not always coincide with the development of resistance to micro-organisms.

L16 ANSWER 56 OF 67 MEDLINE

92221681 Document Number: 92221681. PubMed ID: 1373261. Multiple administration with interleukin-2 potentiates antigen-specific responses to subunit vaccination with bovine herpesvirus-1 glycoprotein IV. Hughes H P; Campos M; van Drunen Littel-van den Hurk S; Zamb T; Sordillo L M; Godson D; Babiuk L A. (Veterinary Infectious Disease Organization, Saskatoon, Saskatchewan, Canada.) VACCINE, (1992) 10 (4) 226-30. Journal code: 8406899. ISSN: 0264-410X. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Interleukin-2 has been described as an effective adjuvant for a number of antigens in different host species. Previously, we demonstrated the adjuvant activity of recombinant bovine IL-2 with a glycoprotein IV (gIV) subunit vaccine from bovine herpesvirus type-1 (BHV-1). In the present study, primary antibody responses were assessed in cattle immunized with either 2 or 50 micrograms of gIV, and treated with multiple doses of IL-2 or combinations of IL-2 and IFN-alpha or IL-2 and IFN-gamma. IL-2 was able to augment significantly antibody responses detected by either ELISA or virus neutralization. More significantly, IL-2 was able to enhance antibody titres in animals immunized with only 2 micrograms gIV to levels similar to those immunized with 50 micrograms gIV in the absence of IL-2. For optimal stimulation, multiple injections of IL-2 and Avridine had to be used in the formulation; other oil adjuvants or IL-2 alone could not induce a primary serum antibody response. Addition of IFN-alpha or IFN-gamma to the IL-2/gIV/Avridine formulation did not affect any of the immune parameters tested. As IFN-alpha is an effective immunoprophylactic agent for infectious bovine rhinotracheitis (IBR), combination vaccine-immunoprophylaxis may become feasible using IL-2 as a co-adjuvant. Thus, extremely low doses of antigen and only one immunization may be an effective vaccine given in combination with interferon prophylactic treatment.

L20 ANSWER 14 OF 14 MEDLINE
89002784 Document Number: 89002784. PubMed ID: 3048654. In vivo effects of recombinant human interleukin 2 on antitumor and antiviral natural immunity in induced or natural murine immunodeficiency states. Butler L D; Browne C P; Layman N K; Riedl P; Tang J; Marder P; DeLong D; Manetta J; Bobbitt L; Strnad J; +. (Department of Immunology Research, Lilly Research Laboratories, Indianapolis, Indiana 46285.) CANCER RESEARCH, (1988 Nov 1) 48 (21) 6081-9. Journal code: 2984705R. ISSN: 0008-5472. Pub. country: United States. Language: English.
AB We have examined the ability of in vivo treatment of mice with recombinant interleukin 2 (rIL-2) to affect natural immunity measured against tumor (YAC-1) or virally infected (herpes simplex type 1) target cells. rIL-2 treatment leads to significant increases in natural killer/lymphocyte-activated killer (NK/LAK) function and spleen cells recovered. This effect is dose dependent and strain related. The latter parameter correlated with the pretreatment NK activity level of the strain. The rIL-2 induced NK/LAK augmentation is also kinetically restricted as treatment must have occurred within 48-72 h of assay to be effective. The rIL-2 therapy effectively enhances both antitumor and antiviral NK/LAK activity and results in a noticeable increase in asialo-GM1-positive cells in the spleens of treated mice as well as a significant increase in IL-2 receptor expression as monitored by either cytometry or radioligand binding. In vivo treatment of mice with an antibody directed to the ASGM1 determinant effectively reduces the rIL-2 augmentation of both antitumor and antiviral activity even though this treatment does not affect the pretreatment level of antiviral activity. Various natural and induced immunodeficiency states (immunotherapy, irradiation, immunosuppressive drugs, cytoreductive drugs) have been examined for the ability of in vivo treatment with rIL-2 to enhance NK/LAK activity. In vivo rIL-2 administration is differentially effective in enhancing NK/LAK activity in these situations. Notably, in these induced immunodeficiency states, although NK/LAK activity is commonly enhanced, the number of spleen cells recovered often is only marginally affected. Thus, as expected, a limiting aspect in this use of a natural immunomodulator is the number of potentially responsive cells present in the immunodeficiency condition. In addition, correlations between rIL-2 effect, several of the immunodeficiency states, and vascular leak syndrome are briefly discussed.

L20 ANSWER 13 OF 14 MEDLINE
94132539 Document Number: 94132539. PubMed ID: 8301059. Pilot study of natural human interleukin-2 in patients with chronic hepatitis B. Immunomodulatory and antiviral effects. Tilg H; Vogel W; Tratkiewicz J; Aulitzky W E; Herold M; Gruber M; Geissler D; Umlauft F; Judmaier G; Schwulera U; +. (Department of Internal Medicine, Innsbruck University, Austria.) JOURNAL OF HEPATOLOGY, (1993 Sep) 19 (2) 259-67. Journal code: 8503886. ISSN: 0168-8278. Pub. country: Ireland. Language: English.
AB Ten patients with chronic hepatitis B received increasing doses of nIL-2 (30,000 U, 100,000 U, 300,000 U, 1.0 million U) subcutaneously in a phase I trial. Each dose was applied once per week over 3 weeks. Serum samples were taken before and 2, 12, 24, 48 and 72 h after the first application of each dose level. Serum concentrations of interleukin-1 (IL-1), IL-2, IL-6, interferon-alfa (IFN-alpha), IFN-gamma, tumor necrosis factor-alpha (TNF-alpha) and GM-CSF as well as the cytokine-dependent serum components neopterin, beta-2-microglobulin (B2M), C-reactive protein (CPR), soluble IL-2-receptor (sIL-2R) and 2'-5'-oligoadenylate synthetase (2-5 OA) were assayed using ELISAs and RIAs. None of the samples tested contained measurable cytokine levels other than IL-2. A low and non-toxic dose of 300,000 U nIL-2 was already biologically active with induction of neopterin, B2M and sIL-2R. Dose-dependent changes peaked 24-48 h after application. The same patients were then enrolled in a phase II trial.

Treatment in five of the patients was continued twice per week for 3 months with a biologically active dose of 300,000 U nIL-2 subcutaneously. Two of these patients as well as another five patients from the original group were treated with 1.0 million U nIL-2 subcutaneously, twice weekly for 3 months. **Neither a biologically active but non-toxic dose of 300,000 U nIL-2, nor a toxic dose of 1.0 million U resulted in permanent clearance of hepatitis B early antigen (HBeAg)**.(ABSTRACT TRUNCATED AT 250 WORDS)

L20 ANSWER 12 OF 14 MEDLINE
94157475 Document Number: 94157475. PubMed ID: 8113740. Modulation of antiviral immune responses by exogenous cytokines: effects of tumour necrosis factor-alpha, interleukin-1 alpha, interleukin-2 and interferon-gamma on the immunogenicity of an inactivated rabies vaccine. Schijns V E; Claassen I J; Vermeulen A A; Horzinek M C; Osterhaus A D. (Department of Infectious Diseases and Immunology, Veterinary Faculty, University of Utrecht, The Netherlands.) JOURNAL OF GENERAL VIROLOGY, (1994 Jan) 75 (Pt 1) 55-63. Journal code: 0077340. ISSN: 0022-1317. Pub. country: ENGLAND: United Kingdom. Language: English.
AB In vivo administration of exogenous cytokines may influence elicited immune responses, and hence may change the efficacy of a vaccine. We investigated the effects of tumour necrosis factor-alpha (TNF-alpha), interleukin-1 alpha (IL-1 alpha), interleukin-2 (IL-2) and interferon-gamma (IFN-gamma) on the immune response elicited by inactivated rabies virus vaccine in a mouse model. Each of the cytokines increased virus-specific IgG responses after primary and after secondary immunization. A single dose of 1.3 ng TNF-alpha or IL-1 alpha, when injected shortly before vaccination, only marginally stimulated resistance to challenge infection (four- and seven-fold, respectively) without enhancing virus neutralizing antibody (VNAb) responses. In contrast, a single injection of 10(3) units of IFN-gamma or **five daily injections of 1.6 micrograms IL-2 increased vaccine dilutions protecting 50% of mice (PD50 values) 77- to 50-fold, respectively, with a concomitant enhancement of VNAb**. At a 1:10,000 dilution of a standard inactivated rabies vaccine preparation both IFN-gamma and IL-2 increased protective immunity without enhancing VNAb responses; in non-vaccinated animals this treatment had no effect on resistance to challenge. Combined administration of IFN-gamma and IL-2 synergistically enhanced VNAb responses. In contrast to the other cytokines tested, IFN-gamma preferentially stimulated virus-specific IgG2a production. It also augmented the vaccine-induced priming of rabies virus-specific splenocyte proliferation. These results document that certain cytokines alone or in combination are potent immunological adjuvants which may direct and modulate immunization-induced antiviral immune responses.

L20 ANSWER 8 OF 14 MEDLINE
96283750 Document Number: 96283750. PubMed ID: 8721559. Consensus symposium on combined antiviral therapy; overview of interferon and IL-2 combinations for the treatment of HIV infection. Sneller M C. (Laboratory of Immunoregulation, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD 20892, USA.) ANTIVIRAL RESEARCH, (1996 Jan) 29 (1) 105-9. Journal code: 8109699. ISSN: 0166-3542. Pub. country: Netherlands. Language: English.
AB Among the immunomodulatory cytokines that have been evaluated for the treatment of HIV disease, alpha-interferon and interleukin-2 (IL-2) have been the most extensively studied. Monotherapy with alpha-interferon is effective therapy for HIV-associated Kaposi's sarcoma (KS) in patients with CD4 counts > 150 cells/mm3. However, the doses necessary to achieve a significant anti-tumor effect are often poorly tolerated. Combination therapy with alpha-interferon and zidovudine is associated with

dose-limiting toxicities and an anti-tumor effect similar to that of higher dose alpha-interferon monotherapy. The combination of alpha-interferon and zidovudine can synergistically inhibit HIV replication in vitro; however, in vivo results suggest the anti-HIV effect of this combination is no greater than that seen with zidovudine monotherapy. Whether combination of interferon-alpha and other antiviral drugs will be useful in the treatment of HIV infection remains to be seen. Recent studies employing **intermittent courses of IL-2 combined with continuous antiretroviral therapy indicate that sustained rises in CD4 counts can be achieved. The ability of IL-2 therapy to result in a sustained rise in CD4 counts is critically dependent on the pre-treatment CD4 count**. The immunologic and clinical significance of these IL-2-induced increases in CD4 counts is unknown. Larger, controlled trials are currently underway to evaluate the role of intermittent IL-2 therapy in HIV infection.

L20 ANSWER 5 OF 14 MEDLINE
2000112500 Document Number: 20112500. PubMed ID: 10647974. A risk-benefit assessment of interleukin-2 as an adjunct to antiviral therapy in HIV infection. Piscitelli S C; Bhat N; Pau A. (Clinical Center Pharmacy Department, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland 20892, USA.. spisc@nih.gov) . DRUG SAFETY, (2000 Jan) 22 (1) 19-31. Ref: 58. Journal code: 9002928. ISSN: 0114-5916. Pub. country: New Zealand. Language: English.

AB Immunomodulation has become a major focus of HIV research in an effort to augment, boost or restore the patient's damaged immune system. Recombinant interleukin-2 is currently being studied in phase II/III trials in HIV-infected patients. Several clinical studies have demonstrated that intermittent regimens are associated with marked rises in CD4+ cell counts without an increase in viral load. Most of these studies employ 5 consecutive days of interleukin-2 therapy by continuous intravenous infusion or subcutaneous injection, repeated every 8 weeks. An alternative strategy is the daily administration of low doses of interleukin-2, but clinical experience with this regimen is limited. Interleukin-2 administration can adversely affect virtually every organ system, requiring aggressive supportive care. A variety of administration strategies and interventions are being evaluated to minimise toxicity. Currently, no clinical end-point data are available for interleukin-2 in HIV-infected patients. Until phase III studies are completed, interleukin-2 can be used in the research setting as an immunomodulator and adjunct to antiretroviral therapy. Its potential to activate latently infected cells and promote HIV eradication from reservoir sites is also an important area for further study. If clinical benefit can be demonstrated, interleukin-2 could be useful as an adjunct to antiretroviral therapy if adverse effects can be minimised and therapy can be given infrequently on an outpatient basis.

L20 ANSWER 4 OF 14 MEDLINE
2001231094 Document Number: 21219021. PubMed ID: 11319683. Efficacy of low-dose intermittent subcutaneous interleukin (IL)--2 in antiviral drug--experienced human immunodeficiency virus--infected persons with detectable virus load: a controlled study of 3 il-2 regimens with antiviral drug therapy.
Tambussi G; Ghezzi S; Nozza S; Vallanti G; Magenta L; Guffanti M; Brambilla A; Vicenzi E; Carrera P; Racca S; Soldini L; Gianotti N; Murone M; Veglia F; Poli G; Lazzarin A. (Clinic of Infectious Diseases, San Raffaele Scientific Institute, 20137, Milan, Italy.. giuseppe.tambussi@hsr.it) . JOURNAL OF INFECTIOUS DISEASES, (2001 May 15) 183 (10) 1476-84. Journal code: 0413675. ISSN: 0022-1899. Pub. country:

United States. Language: English.

AB To evaluate the safety and efficacy of 3 regimens of intermittent subcutaneous (sc) interleukin (IL)--2 in a phase 2 study, 61 antiviral drug-experienced human immunodeficiency virus (HIV)--positive patients were randomly assigned to one of the following study arms: antiretroviral therapy (ART) plus IL-2 (12 million IU [MIU] by continuous intravenous infusion, followed by 7.5 MIU twice a day, sc, every 8 weeks); ART plus IL-2 (7.5 MIU twice a day, sc, every 8 weeks); ART plus IL-2 (3 MIU twice a day, sc, every 4 weeks); or ART alone. **A significant increase of circulating CD4 cells was observed in IL-2--treated subjects**, compared with those given ART alone. Low doses of IL-2 were better tolerated. Despite the incomplete suppression of viral replication, IL-2 with ART did not increase either plasma viremia or cell-associated HIV DNA levels. Low doses of intermittent sc IL-2 induced a stable increase of peripheral CD4 cells that was indistinguishable from those associated with higher, less well-tolerated doses of IL-2.

L22 ANSWER 41 OF 44 MEDLINE
89264594 Document Number: 89264594. PubMed ID: 2786210.
Interleukin 2 acts as an adjuvant to increase the potency of inactivated rabies virus vaccine. Nunberg J H; Doyle M V; York S M; York C J. (Department of Microbial Genetics, Cetus Corporation, Emeryville, CA 94608.) PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1989 Jun) 86 (11) 4240-3. Journal code: 7505876. ISSN: 0027-8424. Pub. country: United States. Language: English.

AB Interleukin 2 (IL-2) occupies a central position in the cascade of events involved in the immune response. We were interested in determining whether IL-2 could function as an adjuvant to vaccination, to increase the immune response to vaccine immunogens. Using the National Institutes of Health test for rabies vaccine potency, we found that daily systemic administration of IL-2 in conjunction with inactivated rabies virus can increase the potency of vaccination in outbred mice at least 25-fold, as measured by survival following challenge with virulent rabies virus. Enhanced protection is not correlated with an increase in virus-neutralizing antibody titers, and we suggest that IL-2 acts to increase the cellular immune response to vaccination.

L22 ANSWER 31 OF 44 MEDLINE
92221677 Document Number: 92221677. PubMed ID: 1561827.
Liposome-formulated interleukin-2 as an adjuvant of recombinant HSV glycoprotein gD for the treatment of recurrent genital HSV-2 in guinea-pigs. Ho R J; Burke R L; Merigan T C. (Department of Medicine, Stanford University School of Medicine, CA 94305.) VACCINE, (1992) 10 (4) 209-13. Journal code: 8406899. ISSN: 0264-410X. Pub. country: ENGLAND: United Kingdom. Language: English.

AB The use of interleukin-2 (IL-2) as an adjuvant to enhance an antigen-induced immunotherapeutic effect was investigated using guinea-pigs with established HSV-2 infection. Animals treated with four weekly doses of liposome-formulated IL-2 (2.7 x 10(5) U kg-1 dose) overlapping two biweekly doses of an HSV-recombinant glycoprotein D (rgD) treatment demonstrated approximately 70% reduction in HSV-2 recurrent disease compared with placebo (p less than 0.005). Combination therapy rgD plus liposome-formulated IL-2 exhibited approximately 30% greater therapeutic effect than either agent alone (p less than 0.05). Liposome formulation of IL-2 was essential to elicit the adjuvant effect. Identical biweekly dosing or more frequent daily dosing of soluble IL-2 did not produce additional therapeutic effects, suggesting the role of liposome targeting to lymph nodes. Although rgD plus liposome-formulated IL-2 induced a marginal early antibody response to rgD, there was no significant increase in overall antibody response. Combination therapy increased the frequency of minimally positive HSV lymphoproliferative

response.

L22 ANSWER 23 OF 44 MEDLINE
95264752 Document Number: 95264752. PubMed ID: 7745993. Adjuvant effect of low-dose interleukin-2 on antibody response to influenza virus vaccination in healthy elderly subjects. Provinciali M; Di Stefano G; Colombo M; Della Croce F; Gandolfi M C; Daghetta L; Anichini M; Della Bitta R; Fabris N. (Immunology Center, INRCA Gerontology Research Department, Ancona, Italy.) MECHANISMS OF AGEING AND DEVELOPMENT, (1994 Dec 16) 77 (2) 75-82. Journal code: 0347227. ISSN: 0047-6374. Pub. country: Ireland. Language: English.

AB It is well known that immune efficiency is frequently deteriorated in elderly people. The age-diminished antibody response to T-cell dependent antigens, such as influenza virus antigens, may explain the low protection offered by influenza vaccination in the elderly population. To investigate the possibility of increasing the antibody response to influenza virus vaccinations, we have conducted a nursing home-based study on the efficacy of IL-2. Seventy-five institutionalized elderly subjects (82 +/- 8 years) were enrolled in the study in the course of winter season 1991-1992. Thirty-nine subjects were treated with three subcutaneous daily injections of interleukin-2 (IL-2, 1 x 10(6) I.U./day) before vaccination and their antibody response was compared to that of 36 aged people receiving the vaccine only. An increased antibody response against influenza virus was present in vaccine plus IL-2 treated subjects ($P < 0.001$) but not in subjects treated with vaccine only. The number of protected subjects 45 days after vaccination was increased only in the IL-2-treated group ($P = 0.045$). The low-dose of IL-2 administered and the short-term treatment allowed a good tolerance to the IL-2 injection. In conclusion, the low-dose IL-2 treatment represents an effective means of inducing antibody response to influenza virus antigens in elderly subjects without appreciable toxicity.

L10 ANSWER 4 OF 83 USPATFULL on STN
2003:20210 Stimulation of immune response with low doses of cytokines.
Smith, Kendall A., New York, NY, United States
Cornell Research Foundation, Inc., Ithica, NY, United States (U.S. corporation)
US 6509313 B1 20030121
APPLICATION: US 1996-646098 19960507 (8) <--
DOCUMENT TYPE: Utility; GRANTED.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A method of activating the immune system of a subject comprises the chronic administration of low doses of an agent having cytokine activity, including natural and recombinant cytokines, fragments, analogues, fusion proteins, and derivatives thereof, that are pharmaceutically acceptable, and their mixtures with other biologically active agents and formulation ingredients. The agent is provided as a unit dosage form, in systemic and topical product form, as an implant, inhalant, transdermal delivery device, and ultrasound and electrotransport devices, as well as in the form of a kit for self-administration.

CLM What is claimed is:

1. **A method of administering or applying to, or self-applying by, a subject a composition comprising an agent selected from natural and recombinant IL-2** and mixtures thereof, for a period greater than three months under conditions effective to release an amount effective to activate high affinity interleukin and/or interferon receptors and **enhance immune function in the absence of the symptoms of toxicity Grade 1 or higher**, as depicted in FIG. 1A and FIG. 1B.

2. The method of claim 1, wherein the composition further comprises a physiologically acceptable carrier.

3. The method of claim 2, wherein the carrier comprises a pharmaceutically or veterinarily acceptable carrier.

4. The method of claim 1, wherein the composition is administered, applied, self-administered, or self-applied subcutaneously, intramuscularly, intradermally, intralymphatically, intra tumor, transdermally, intracavitarily, transbuccally, transpulmonarily, transmucosally, orally, intra nasally, intra vaginally, intra anally, intra buccally, sublingually, by inhalation, or by implant.

5. The method of claim 1, further comprising adjusting the agent's dose by monitoring the blood concentration of the agent, the % saturation of the high affinity cytokine receptors, or the blood count of at least a cell type selected from the group consisting of circulating lymphocytes, monocytes and polymorphonuclear leukocytes.

6. The method of claim 1, wherein the composition is self-administered.

7. The method of claim 1, wherein the composition is administered, applied, self-administered, or self-applied in the form of a powder, a tablet, a capsule, a dragee, a cream, a solution, a suspension, an emulsion, a gel, a spray, a controlled release formulation, liposome or other micelles, or combinations or mixtures thereof and, if needed, is formulated prior to administration, application, self-administration, or self-application.

8. The method of claim 7, wherein the composition is a controlled release formulation.

9. The method of claim 7, wherein the composition is an inhalable formulation, and is administered, applied, self-administered, or self-applied by means of an inhaler.

10. The method of claim 7, wherein the composition is a topical formulation, further comprising a carrier or diluent for the agent suitable for topical delivery, and optionally an ingredient selected from the group consisting of buffers, salt forming acids and bases, perfumes, colorants, emollients, adjuvants, single or multiple enteric coatings, copolymers, microporous or semi-permeable membranes, enzyme inhibitors, mucoadhesives, chelating agents, particulate systems, viral envelope proteins, liposomes and other micelles, emulsifiers, lipoproteins and other fatty acid derivatives, surfactants, bile salts, hydrophilic, neutral, and hydrophobic polymers and co-polymers, hydrogels, biodegradable polymers and co-polymers, and an additional bioactive agent consisting of anti-viral agents in an amount and under conditions effective to facilitate the passage onto and through the subject's dermal, mucosal or pulmonary surface of a daily dose of the agent.

11. The method of claim 10, wherein the topical formulation is a cream, an ointment, a solution, a gel, a powder, a suspension, an emulsion, encapsulated particles or mixtures thereof.

12. The method of claim 11, wherein a solution or suspension of the composition is comprised in, and delivered from, a compartment of a transdermal device.

13. The method of claim 12, wherein the device is an electrotransport or ultrasound device.

14. The method of claim 7, wherein the composition is formulated as a vaccine.

15. The method of claim 1, wherein the composition is in solid form, and is formulated prior to administration, application, self-administration, or self-application.

16. The method of claim 15, wherein the composition is in lyophilized form.

17. The method of claim 1, wherein the composition is in liquid form.

18. The method of claim 1, wherein the composition is administered, applied, self-administered, or self-applied as a therapeutic product comprising the agent, which when administered or applied to, or self-administered or self-applied by, the subject releases the desired amount of the agent over a pre-determined period of time effective to activate, and maintain activated for the period of time, high affinity agent receptors without producing substantial toxicity of grade 1 or higher, as depicted in FIG. 1A and FIG. 1B.

19. The method of claim 18, wherein the product is in the form of a patch, an implant or a suppository.

20. The method of claim 1, wherein the composition further comprises an ingredient selected from the group consisting of carriers, diluents, buffers, salt forming acids and bases, perfumes, colorants, emollients,

adjuvants, single or multiple enteric coatings, copolymers, midroporous or semi-permeable membranes, enzyme inhibitors, mucoadhesives, chelating agents, particulate systems, viral envelope proteins, liposomes and other micelles, emulsifiers, lipoprotein and other fatty acid derivatives, surfactants, bile salts, hydrophilic, neutral, and hydrophobic polymers and co-polymers, hydrogens, biodegradable polymers and co-polymers, and anti-inflammatories, an additional bioactive agent consisting of anti-viral agents.

21. The method of claim 1, wherein the composition is parenteral formulation.

22. The method of claim 21, wherein the parenteral formulation is an injectable formulation.

23. The method of claim 22, wherein the injectable formulation is administered, applied, self-administered, or self-applied subcutaneously, intravenously, or intraperitoneally.

24. The method of claim 1, wherein the agent is present in an amount of about 0.0001 to 50 wt % of the composition.

25. The method of claim 1, wherein the subject is a normal subject or a subject afflicted with a condition associated with a viral microorganism.

26. The method of claim 25, wherein the **subject is HIV seropositive**, and the composition is administered in an amount and under conditions which substantially avoid increasing the count of circulating microorganism.

27. The method of claim 1, wherein the subject is an animal.

28. The method of claim 27, wherein the animal is a human.

29. The method of claim 1, wherein the amount of the agent administered is effective to elevate the blood count of at least one blood cell type selected from the group consisting of circulating lymphocytes, monocytes and polymorphonuclear leukocytes.

30. The method of claim 29, wherein the amount of the agent administered is effective to elevate the blood count of at least one blood cell selected from the group consisting of circulating T-cells, B-cells, NK cells, monocytes, eosinophils, neutrophils, basophils and antigen-presenting cells.

31. The method of claim 1, wherein the composition is administered as an implant.

32. The method of claim 1, further comprising administering or applying to, self-administering or self-applying by, the subject one or more ant-viral agents.

33. The method of claim 32, wherein the anti-viral agents are selected from the group consisting of nucleotide analogues and protease inhibitors.

34. The method of claim 33, wherein the subject is a normal subject or a **subject afflicted with a condition associated with a viral microorganism**.

35. The method of claim 34, **wherein the subject is HIV seropositive**, and the composition is administered in an amount and under conditions which substantially avoid increasing the count of circulating microorganism.

36. The method of claim 34, **wherein the subject is hepatitis-C seropositive**, and the composition is administered in an amount and under conditions which substantially avoid increasing the count of circulating microorganism.

37. The method of claim 32, wherein the subject is administered, applied, self-administers or self-applies, one or more anti-viral agents selected from the group consisting of zidovudine (AZT), 2',3'-dideoxyinosine (ddI), 3'-azido-2',3'-dideoxythymidine, d4T, acyclovir, 1,3-dihydro-2-propoxy-methyquanine (gancyclovir), ribavirin, dideoxycytidine (ddC), lamivudine (3TC), and enzyme inhibitors.

38. The method of claim 37, wherein the subject is administered or applied, self-administers or self-applies one or more enzyme inhibitors, and the enzyme inhibitors comprise protease inhibitors.

39. The method of claim 38, wherein the protease inhibitors are saquinovir or invirase.

40. The method of claim 39, wherein the subject is administered or applied, self-administers or self-applies one or more anti-viral agents, and the anti-viral agents are selected from the group consisting of zidovudine (AZT), lamivudine (3TC), d4T, invirase and combinations thereof.

41. The method of claim 40, wherein the anti-viral agent combinations administered, applied, self-administered or self-applied comprise zidovudine (AZT), lamivudine (3TC), and d4T, or zidovudine (AZT), lamivudine (3TC), and invirase.

42. The method of claim 41, wherein the anti-viral agent combination administered, applied, self-administered or self-applied comprises zidovudine (AZT), lamivudine (3TC), and invirase, and zidovudine is administered, applied, self-administered or self-applied at about 600 mg/day, lamivudine (3TC) at about 300 mg/day, and invirase at about 600 mg/day.

43. A method of administering or applying to, or self-administering or self-applying by, a subject a composition comprising an agent selected from natural and recombinant IL-2 and mixtures thereof, for a period greater than three months under conditions effective to release an amount effective to activate high affinity IL-2 receptors and enhance immune function in the absence of the symptoms of toxicity Grade 1 or higher, as depicted in FIG. 1A abd FIG 1B.

44. The method of claim 43, wherein the composition further comprises a physiologically acceptable carrier.

45. The method of claim 43, wherein the composition is administered, applied, self-administered, or self-applied subcutaneously, intramuscularly, intradermally, intralymphatically, intratumor, transdermally, intracavitarily, transbuccally, transpulmonarily, transmucosally, orally, intranasally, intravaginally, intraanally,

intrabuccally, sublingually, by inhalation, or by implant.

46. The method of claim 43, further comprising adjusting the agent's dose by monitoring the blood concentration of the agent, the % saturation of the high affinity IL-2 receptors, or the blood count of at least a cell type selected from the group consisting of circulating lymphocytes, monocytes and polymorphonuclear leukocytes.

47. The method of claim 43, wherein the composition is administered, applied, self-administered, or self-applied as a therapeutic product comprising the agent, which when administered or applied to, or self-administered or self-applied by, the subject releases the desired amount of the agent over a pre-determined period of time effective to activate, and maintain activated for the period of time, high affinity agent receptors without producing substantial toxicity symptoms of grade 1 or higher as depicted in FIG. 1A and 1B.

48. The method of claim 43, wherein the composition further comprises an ingredient selected from the group consisting of carriers, diluents, buffers, salt forming acids and bases, perfumes, colorants, emollients, adjuvants, single or multiple enteric coatings, copolymers, microporous or semi-permeable membranes, enzyme inhibitors, mucoadhesives, chelating agents, particulate systems, viral envelope proteins, liposomes and other micelles, emulsifiers, lipoproteins and other fatty acid derivatives, surfactants, bile salts, hydrophilic, neutral, and hydrophobic polymers and co-polymers, hydrogels, biodegradable polymers and co-polymers, and anti-inflammatories, an additional bioactive agent consisting of anti-viral agents.

49. The method of claim 43, wherein the agent is present in an amount of about 0.0001 to 50 wt % of the composition.

50. The method of claim 43, wherein the subject is a normal subject or a subject afflicted with a condition associated with a viral microorganism.

51. The method of claim 43, wherein the subject is HIV seropositive, and the composition is administered in an amount and under conditions which substantially avoid increasing the count of circulating microorganism.

52. The method of claim 43, wherein the subject is a human.

53. The method of claim 43, wherein the amount of the agent administered is effective to elevate the blood count of at least one blood cell type selected from the group consisting of circulating lymphocytes, monocytes and polymorphonuclear leukocytes.

54. The method of claim 43, wherein the amount of the agent administered is effective to elevate the blood count of at least one blood cell selected from the group consisting of circulating T-cells, B-cells, NK cells, monocytes, eosinophils, neutrophils, basophils and antigen-presenting cells.

55. The method of claim 43, further comprising administering or applying to, self-administering or self-applying by, the subject a bioactive agent consisting of anti-viral agents.

56. The method of claim 43, wherein the subject is administered or applied, or self-administers, or self-applies, the agent and one or more

bioactive agents consisting of anti-viral agents.

57. A method of increasing and/or maintaining the count of circulating blood cells selected from the group consisting of lymphocytes, monocytes, and polymorphonuclear leukocytes, comprising conducting the method of claim 43, wherein the composition is administered, applied, self-administered, or self-applied for a period greater than three months under conditions effective to release an amount effective to increase and/or maintain circulating blood cell count.

L10 ANSWER 29 OF 83 USPATFULL on STN
2001:25423 Immunologic enhancement with intermittent interleukin-2 therapy.
Lane, H. Clifford, Bethesda, MD, United States
Kovacs, Joseph A., Potomac, MD, United States
Fauci, Anthony S., Washington, DC, United States
The United States of America as represented by the Department of Health and Human Services, Washington, DC, United States (U.S. corporation)
US 6190656 B1 20010220
APPLICATION: US 1997-922218 19970902 (8) <--
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A method for activating a mammalian immune system entails a series of IL-2 administrations that are effected intermittently over an extended period. Each administration of IL-2 is sufficient to allow spontaneous DNA synthesis in peripheral blood or lymph node cells of the patient to increase and peak, and each subsequent administration follows the preceding administration in the series by a period of time that is sufficient to allow IL-2 receptor expression in peripheral or lymph node blood of the patient to increase, peak and then decrease to 50% of peak value. This intermittent IL-2 therapy can be combined with another therapy which targets a specific disease state, such as an anti-retroviral therapy comprising, for example, the administration of AZT, ddI or interferon alpha. In addition, IL-2 administration can be employed to facilitate in situ transduction of T cells in the context of gene therapy. By this approach the cells are first activated in vivo via the aforementioned IL-2 therapy, and transduction then is effected by delivering a genetically engineered retroviral vector directly to the patient.

CLM What is claimed is:
1. **A method for administration of interleukin-2 (IL-2) to increase immune function in a human subject, comprising:** (a) **administering an amount of IL-2 to a human subject in a first administration in an amount that is sufficient to increase the CD4 count in the subject as compared with the count prior to IL-2 administration,** wherein the administration of IL-2 is continuous over a period of time that is sufficient to allow spontaneous DNA synthesis in peripheral blood or lymph node cells of the subject to increase and peak; (b) measuring the DNA synthesis in cells obtained from the subject during the administration period, wherein a time period of an increase or peak in DNA synthesis is indicative of an optimal duration of interleukin-2 (IL-2) administration; (c) administering a subsequent amount of IL-2 to the subject that is sufficient to increase the CD4 count in the subject as compared to the count prior to IL-2

administration, wherein the subsequent administration of IL-2 is continuous over a period of time that is sufficient to allow spontaneous DNA synthesis in peripheral blood or lymph node cells of the subject to increase and peak, and wherein the subsequent administration of IL-2 follows the first administration of IL-2 by a period of time that is sufficient to allow IL-2 receptor expression in peripheral blood or lymph node cells of the subject to increase as compared to the level of expression prior to IL-2 administration, peak then decrease to 50% of peak value; and (d) measuring the DNA synthesis in cells obtained from the subject during the subsequent administration, wherein a time period of an increase or peak in DNA synthesis is indicative of an optimal duration of IL-2 administration; and (e) discontinuing administration of the subsequent amount of L2 administration at about the time of peak in DNA synthesis.

2. The method of claim 1, wherein IL-2 is administered in the first administration for a period of time from about one day to about 14 days and the subsequent administration of IL-2 begins at least 4 weeks after the end of the first administration of IL-2.

3. The method of claim 2, wherein the IL-2 is administered for about 5 days.

4. The method of claim 1, wherein the IL-2 is administered at a **dosage of from 1.8 to 24 MU/day.**

5. The method of claim 1, wherein the subject is an **HIV-infected subject.**

6. The method of claim 1, wherein the IL-2 administration is effected by continuous infusion.

7. The method of claim 1, wherein the IL-2 administration is effected by a series of subcutaneous injections.

8. The method of claim 7, wherein the IL-2 administration is effected by from 1-3 subcutaneous injections per day.

9. The method of claim 1, wherein IL-2 is administered for a period of time from about one day to about 14 days.

10. A method of activating the immune system of a subject, comprising: administering to the subject an amount of IL-2 sufficient to increase a level of helper/inducer T-cell function in the subject, wherein the IL-2 is administered in a series of successive continuous administrations, wherein each of the continuous administrations extend over a period of from 1 day to 2 weeks, and successive administrations are separated by a period of time of at least 4 weeks, wherein a duration of the continuous infusion is determined by measuring an increase in lymphocyte formation, and discontinuing administration of the IL-2 after a peak of lymphocyte formation has been detected.

11. The method of claim 10, wherein the peak of lymphocyte formation is determined by measuring lymphocyte blast formation.

12. The method of claim 10, wherein the peak of lymphocyte formation is determined by measuring DNA synthesis.

13. The method of claim 10, wherein the subject is infected with the human immunodeficiency virus.

14. A method of stimulating an immune response in a subject, comprising; administering to the subject a therapeutically sufficient dose of IL-2 for a sufficient period of time to stimulate an increase in a CD4 count of the subject compared to prior to administration of the IL-2, wherein the sufficient period of time is determined by identifying peak activation of the immune system by evaluating a parameter of T cell proliferation, and discontinuing administration of the IL-2 when or after it is determined that peak activation has already occurred.

15. The method of claim 14, wherein peak activation of the immune system is determined by measuring lymphocyte blast formation.

16. The method of claim 15, wherein peak activation of the immune system is determined by measuring DNA synthesis in peripheral blood or lymph node cells of the subject.

17. The method of claim 14, further comprising repeatedly administering the therapeutically sufficient dose of IL-2 to the subject after a sufficient period of time for the subject's immune system to pass through a refractory period of relative resistance to stimulation with IL2.

18. The method of claim 17, further comprising determining that the subject's immune system has passed through the refractory period by determining that IL-2 receptor expression in peripheral blood or lymph node cells of the subject have decreased at least 50% from a peak value of IL-2 receptor expression during IL-2 administration.

L10 ANSWER 31 OF 83 USPATFULL on STN
2001:1473 Biological applications of new peptides of IL-2 and derivatives and use as therapeutic agents.
Theze, Jacques, Paris, France
Eckenberg, Ralph, Germain en Laye, France
Moreau, Jean-Louis, Paris, France
Mazie, Jean-Claude, Asnieres-sur-Seine, France
Institut Pasteur, Paris, France (non-U.S. corporation)
US 6168785 B1 20010102
APPLICATION: US 1998-116594 19980716 (9) <--
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention relates to the use as therapeutic agents of IL-2 peptides and derivatives having biological activity and anti-IL-2 antibodies which mimic or modulate the biological activities of IL-2. The invention also relates to DNA sequences encoding the IL-2 peptides, and to methods of using the IL-2 peptides and derivatives and anti-IL-2 antibodies to modulate or mimic or antagonize the biological activities of IL-2 in vivo and to assay for the presence and activity of the IL-2 receptor.

CLM What is claimed is:
1. A method of inducing in a patient an activity of IL-

2, wherein said activity is selected from the group consisting of stimulation of CD4 cells, stimulation of CD8+ cells, stimulation of NK cells, antiviral activity, antitumor activity, induction of SHC phosphorylation and induction of SHC/MAPK pathway comprising administering to said patient an amount of a peptide not greater than 30 amino acids in length comprising SEQ ID NO:2 sufficient to induce said activities.

2. The method according to claim 1, wherein said activity is useful to treat metastatic melanoma, renal adenocarcinoma, melanoma, colorectal cancer, lung adenocarcinoma, breast cancer, ovarian cancer and viral infections cancer, infectious diseases, HIV infection or autoimmune disorders.

3. The method of claim 1, further comprising administering in admixture with the peptide a cytokine.

4. The method of claim 3, wherein the cytokine is **IL-2** , IL-4, IL-9, or IL-15.

5. The method of claim 3, wherein 1.times.10.sup.6 international units of IL-2 is administered per injection.

6. The method of claim 1, wherein said the patient is infected with **HIV** and where the activity is stimulation of CD4 cells.

L10 ANSWER 39 OF 83 USPATFULL on STN
2000:40633 Method of stimulation of immune response with low doses of IL-2.
Smith, Kendall A., New York, NY, United States
Cornell Research Foundation, Inc., Ithaca, NY, United States (U.S. corporation)
US 6045788 20000404
APPLICATION: US 1996-608516 19960228 (8) <--
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A method of activating the immune system of a subject comprises the chronic administration of low doses of an agent such as IL-2, fusion proteins thereof and derivatives thereof that are pharmaceutically acceptable. The agent is provided as a dermal composition, transdermal delivery device and electrotransport device as well as in the form of a kit for self-administration.

CLM What is claimed is:
1. **A method of chronic stimulation and/or maintenance of immune response, comprising the administration or application or self-application to a subject or the subject's self-administration of a composition comprising an agent selected from the group consisting of natural and recombinant IL-2**, pharmaceutically-acceptable fusion proteins of natural and recombinant IL-2, PEG-natural and -recombinant IL-2, lipid-conjugated natural and recombinant IL-2, therapeutic agent-linked natural and recombinant IL-2 , reduced natural and recombinant IL-2, glycosylated natural and recombinant IL-2, non-glycosylated natural and recombinant IL-2, and mixtures thereof, for a period greater than three months in an amount and under conditions effective to release **about 100,000 to about 500,000 IU IL2/m.sup.2 body**

surface/day or equivalent to about 1,000 to about 500,000 IU IL -2/m.sup.2 body surface/day, the agent having a specific activity or 15.times.10.sup.6 IU/mg protein.

2. The method of claim 1, wherein the composition is administered, applied, self-administered, or self-applied by subcutaneous, intramuscular, intradermal, intralymphatic, intratumor, transdermal, intracavitary, transbuccal, transpulmonary, oral, intranasal, transmucosal, intravaginal, intraanal, intrabuccal, or sublingual administration or application, by inhalation, or by implant.

3. The method of claim 1, wherein the composition is self-administered.

4. The method of claim 1, wherein the composition comprises a controlled release composition.

5. The method of claim 1, further comprising adjusting the amount of the agent administered, applied, self-administered, or self-applied by monitoring the blood concentration of the agent, the % saturation of the high affinity IL-2 receptors, or the blood count of at least a cell type selected from the group consisting of circulating lymphocytes, monocytes, and polymorphonuclear leukocytes.

6. The method of claim 1, wherein the subject is a normal subject or a subject afflicted with a condition associated with a **viral**, bacterial, fungal, and parasitic microorganism, a congenital or acquired immunodeficiency, or a malignancy.

7. The method of claim 6, wherein the subject is **HIV seropositive human**; and the composition is administered applied, self-administered, or self-applied in an amount and under conditions which substantially avoid increasing the count of circulating microorganisms.

8. The method of claim 1, wherein the subject is an animal.

9. The method of claim 8, wherein the animal is a human.

10. The method of claim 1, wherein the amount of the agent administered, allied, self-administered, or self-applied is effective to elevate the count of at least one blood cell type selected from the group consisting of circulating lymphocytes, monocytes, pa polymorphonuclear leukocytes.

11. The method of claim 10, wherein the amount of the agent administered, applied, self-administered, or self-applied is effective to elevate the count of at least one blond cell selected from the group consisting of circulating T-cells, B-cells, NK cells, monocytes, eosinophils, neutrophils, basophils and antigen-presenting cells.

12. The method of claim 1, wherein the administered, applied, self-administered or self-applied composition is in the form of a powder, a tablet, a capsule, a dragee, a cream, a solution, a suspension, an emulsion, a gel, a spray, a liposome or other micelle, or combinations or mixtures thereof, and formulated prior to administration, application, self-administration or self-application.

13. The method of claim 1, wherein the administered or self-applied composition is in solid form, and formulated prior to administration, application, self-administration, or self-application.

14. The method of claim 13, wherein the administered, applied self-administered or self-applied composition is in lyophilized form.

15. The method of claim 1, wherein the administered, applied, self-administered or self-applied composition is in liquid form.

16. The method of claim 1, wherein the composition is administered, applied, self-administered, or self-applied by means of an inhalant.

17. The method of claim 1, wherein the agent is administered, applied, self-administered, or self-applied as a topical composition, further comprising a carrier or diluent for the agent suitable for topical delivery and an ingredient selected from the group consisting of buffers, salt forming acids and bases, perfumes, colorants, emollients, adjuvants, single or multiple enteric coatings, copolymers, microporous or semi-permeable membranes, enzyme inhibitors, mucoadhesives, chelating agents, particulate systems, viral envelope proteins, liposomes and other micelles, emulsifiers, lipoproteins and other fatty acid derivatives, surfactants, bile salts, hydrophilic, neutral, and hydrophobic polymers and co-polymers, hydrogels, biodegradable polymers and co-polymers, and an additional bioactive agent selected from the group consisting of additional lymphokines or cytokines , and fusion proteins of the lymphokines or cytokines, anti-inflammatories, anti-bacterial, anti-viral, anti-fungal, anti-parasitic, anti-metabolic, anti-inflammatory, vasoactive, anti-neoplastic, bronchodilating, local anesthetic, immunomodulating, growth promoting and regenerating agents, enzymatic, hormonal agents, neurotransmitters, and cell receptor proteins and ligands.

18. The method of claim 17, wherein the composition is in the form of a cream, an ointment, a solution, a gel, a powder, a suspension, an emulsion, encapsulated particles or mixtures thereof.

19. The method of claim 17, wherein the agent is present in an amount of about 0.0001 to 50 wt % of the composition.

20. The method of claim 17, wherein the composition comprises a controlled release composition.

21. The method of claim 17, wherein the composition is administered by a transdermal delivery device comprising, in a sterile container, a solid support; and a compartment provided in the solid support, the compartment comprising a solution or suspension of the composition, and having one side permeable thereto; whereby when the permeable side of the compartment is placed in contact with an area of a subject's dermis a desired amount of the agent passes from the device onto, and through, the dermis of the subject, over a pre-determined period of time.

22. The method of claim 21, wherein the device comprises a unit dose of the agent.

23. The method of claim 21, wherein the device further comprises a cover placed on the permeable side of the container; the cover being substantially impermeable to the solution or suspension and removable prior to administration, application, or self-application.

24. The method of claim 21, wherein the device is an electrotransport device, further provided with donor and counter electrodes; external power source and control circuitry; wherein the solution or suspension further comprises electroconducting agents, and when the permeable side of the device is placed in contact with an area of the subject's dermis

and an electric field is applied to the electrodes, a desired amount of the agent passes from the device onto, and through, the dermis of the subject, over a pre-determined period of time.

25. The method of claim 21, wherein the device is an ultrasound device, further provided with ultrasound transducer, external power source and control circuitry; wherein when the permeable side of the device is placed in contact with an area of the subject's dermis and an electric field is applied to the ultrasound generator, a desired amount of the agent passes from the device onto, and through, the dermis of the subject, over a pre-determined period of time.

26. The method of claim 20, wherein the agent is released by an implant, the implant comprising an amount effective to release the desired amount of the agent over a predetermined period of time.

27. The method of claim 1, further comprising administering or applying to the subject or having the subject self-administer or self-apply a bioactive agent selected from the group consisting of additional lymphokines or cytokines, fusion proteins of the lymphokines or cytokines, anti-inflammatory, anti-bacterial, anti-viral, anti-fungal, anti-parasitic, anti-metabolic, vasoactive, anti-neoplastic, bronchodilating, local anesthetic, immunomodulating, growth promoting, regenerating, enzymatic and hormonal agents, neurotransmitters, and cell receptor proteins and ligands.

28. The method of claim 27, wherein the subject is administered, applied, self-administered, or self-applied the agent and a bioactive agent selected from the group consisting of anti-bacterial agents, anti-fungal agents, anti-parasitic agents and anti-viral agents.

29. The method of claim 28, wherein tie bioactive agent comprises one or more anti-viral agents.

30. The method of claim 29, wherein the anti-viral agents are selected from the group consisting of nucleotide analogues and protease inhibitors.

31. The method of claim 30, wherein the subject is administered, applied, self-administers or self-applies, one or more anti-viral agents selected from the group consisting of zidovudine (AZT), 2',3'-dideoxyinosine (ddI), 3'-azido- 2', 3'-dideoxythymidine, d4T, acyclovir, 1,3-dihydro-2-propoxy-methyquanine (gancyclovir), ribavirin, dideoxycytidine (ddC), lamivudine (3TC), and enzyme inhibitors.

32. The method of claim 31, wherein the subject is administered or applied, self-administers or self-applies one or more enzyme inhibitors, and the enzyme inhibitors comprise protease inhibitors.

33. The method of claim 32, wherein the protease inhibitors are saquinovir or invirase.

34. The method of claim 31, wherein the subject is administered or applied, self-administers or self-applies one or more anti-viral agents, and the anti-viral agents are selected from the group consisting of zidovudine (AZT), lamivudine (3TC), d4T, invirase and combinations and mixtures thereof.

35. The method of claim 34, wherein the anti-vital agent combinations administered, applied, self-administered or self-applied comprise zidovudine (AZT), lamivudine (3TC), and d4T, or zidovudine (AZT),

lamivudine (3TC), and invirase.

36. The method of claim 35, wherein the anti-viral agent combination administered, applied, self-administered or self-applied comprises zidovudine (AZT), lamivudine (3TC), and d4T, and zidovudine is administered, applied, self-administered or self-applied at about 600 mg/day, lamivudine (3TC) at about 300 mg/day, and invirase at about 600 mg/day.

37. The method of claim 28, wherein the subject is administered, applied, self-administers or self-applies one or more bioactive agents.

38. The method of claim 37, wherein the bioactive agents comprise anti-bacterial agents.

39. The method of claim 37, wherein the anti-bacterial agents comprise antibiotics.

40. The method of claim 39, wherein the antibiotics are selected from the group consisting of pentamidines, trimethoprim-sulfamethoxazole, sulfonamides, penicillins, cephalosporins, aminoglycosides, tetracyclines, chloramphenicols, and combinations and mixtures thereof.

41. The method of claim 37, wherein the bioactive agents comprise anti-fungal agents.

42. The method of claim 41, wherein the anti-fungal agents are selected from the group consisting of flucytosine, amphotericin B, fluconazole, griseofulvine, and combinations and mixtures thereof.

43. The method of claim 37, wherein the bioactive agents comprise anti-parasitic agents.

44. The method of claim 43, wherein the anti-parasitic agents are selected from the group consisting of pyrimethamine, quinacrine, thiabendazole, levamisol, and combinations and mixtures thereof.

45. The method of claim 37, wherein the bioactive agents comprise anti-metabolic agents.

46. The method of claim 45, wherein the anti-metabolic agents are selected from the group consisting of purine analogues, folic acid analogues, pyrimidine analogues, and combinations and mixtures thereof.

47. A method of chronic stimulation and/or maintenance of immune response, comprising the administration or application to a subject in need of treatment or the subject's self-administration, or self-application of an agent selected from the group consisting of natural and recombinant IL-2, pharmaceutically-acceptable fusion proteins of natural or recombinant IL-2, PEG-natural and recombinant IL-2, lipid-conjugated natural and recombinant L-2, therapeutic agent-linked natural and recombinant IL-2, reduced natural and recombinant IL-2, glycosylated natural and recombinant IL-2, non-glycosylated natural and recombinant IL-2, and mixtures thereof, for a period greater than three months in an amount and under conditions effective to release about 100,000 to about 500,000 IU IL-2 /m.sup.2 body surface/day or equivalent to about 100,000 to about 500,000 IU IL-2/m.sup.2 body surface/day, the agent having a specific activity of 15.times.10.sup.6 IU/mg protein.

48. A method of increasing and/or maintaining the count of circulating blood cells selected from tie group consisting of lymphocytes, monocytes, and polymorphonuclear leukocytes, comprising the administration or application to a subject or the subject's self-administration, or self-application of a composition comprising an agent selected from the group consisting of natural and recombinant IL-2, pharmaceutically acceptable Fusion proteins of natural and recombinant IL-2, PEG-IL-2 natural and recombinant, lipid-conjugated natural and recombinant IL-2, therapeutic agent-linked natural and recombinant IL-2, reduced natural and recombinant IL-2, glycosylated natural and recombinant IL-2, non-glycosylated natural and recombinant IL-2, and mixtures thereof, for a period greater than three months in an amount and under conditions effective to release about 100,000 to about 500,000 IU IL-2 /m.sup.2 body surface/day or equivalent to about 100,000 to about 500,000 IU IL-2/m.sup.2 body surface/day, the agent having a specific activity of 15.times.10.sup.6 IU/mg protein.

49. The method of claim 48, wherein the composition further comprises an ingredient selected from the group consisting of carriers, diluents, buffers, salt forming acids and bases, perfumes, colorants, emollients, adjuvants, single or multiple enteric coatings, copolymers, microporous or semi-permeable membranes, enzyme inhibitors, mucoadhesives, chelating agents, particulate systems, viral envelope proteins, liposomes and other micelles, emulsifiers, lipoproteins and other fatty acid derivatives, surfactants, bile salts, hydrophilic, neutral, and hydrophobic polymers and co-polymers, hydrogels, biodegradable polymers and co-polymers, and anti-inflammatories, an additional bioactive agent selected from the group consisting of additional lymphokines or cytokines, and fusion proteins of the lymphokines or cytokines, anti-inflammatories, anti-bacterial, anti-viral, anti-fungal, anti-parasitic, anti-metabolic, anti-inflammatory, vasoactive, anti-neoplastic, bronchodilating, local anesthetic, immunomodulating, growth promoting and regenerating agents, enzymatic, hormonal agents, neurotransmitters, and cell receptor proteins and ligands.

50. The method of claim 48, wherein the subject is selected from the group consisting of normal subjects and subjects afflicted with a condition associated with a viral, bacterial, fungal, and parasitic microorganism, a congenital and acquired immunodeficiency, and a malignancy.

51. The method of claim 50, wherein the subject is an HIV seropositive human, and the agent is administered, applied, self-administered, or self-applied in an amount and under conditions which avoid increasing the count of circulating microorganisms.

52. A method of administering or applying to a subject an agent selected from the group consisting of natural and recombinant IL-2, pharmaceutically acceptable fusion proteins of natural and recombinant IL-2, PEG-IL-2 natural and recombinant, lipid-conjugated natural and recombinant IL-2, therapeutic agent-linked natural and recombinant IL-2, reduced natural and recombinant IL-2, glycosylated natural and recombinant IL-2 , non-glycosylated natural and recombinant IU-2, and mixtures thereof in the absence of toxicity grade 1 or higher, comprising the administration, application, self-administration, or self-application

for a period greater than three months of a composition comprising the agent in an amount and under conditions effective to release about 100,000 to about 500,000 IU IL-2/m.sup.2 body surface/day or equivalent to about 100,000 to about 500,000 IU IL2/m.sup.2 body surface/day, the agent having a specific activity of 15.times.10.sup.6 IU/mg protein.

53. The method of claim 52, wherein the subject is selected from the group consisting of normal subjects and subjects afflicted with a condition associated with a viral, bacterial, fungal, and parasitic microorganism, a congenital and acquired immunodeficiency, and a malignancy.

54. The method of claim 53, wherein the subject is an HIV seropositive human, and the agent is administered, applied, self-administered, or self-applied in an amount and under conditions which avoid increasing the count of circulating microorganisms.

55. A method of administering or applying to a subject an agent selected from the group consisting of natural and recombinant IL-2, pharmaceutically acceptable fusion proteins of natural and recombinant IL-2, PEG-IL2 natural and recombinant, lipid-conjugated natural and recombinant IL-2, therapeutic agent-linked natural and recombinant IL-2 , reduced natural and recombinant IL-2, glycosylated t in a IL-2, non-glycosylated natural and recombinant IL-2, and mixtures thereof, comprising the administration, application, self-administration, or self-application for a period greater than three months of a therapeutic product comprising the agent, which when administered or applied lo a subject releases an amount of the agent over a pre-determined period of time effective to release about 100,000 to about 500,000 IU IL -2/m.sup.2 body surface/day or equivalent to about 100,000 to about 500,000 IU IL-2/m.sup.2 body surface/day, the agent having a specific activity of 15.times.10.sup.6 IU/mg protein.

56. The method of claim 55, wherein the product further comprises an ingredient selected from the group consisting of carriers, diluents, buffers, salt forming acids and bases, perfumes, colorants, emollients, adjuvants, single or multiple enteric coatings, copolymers, microporous or semi-permeable membranes, enzyme inhibitors, mucoadhesives, chelating agents, particulate systems, viral envelope proteins, liposomes and other micelles, emulsifiers, lipoproteins and other fatty acid derivatives, surfactants, bile salts, hydrophilic, neutral, and hydrophobic polymers and co-polymers, hydrogels, biodegradable polymers and co polymers, and anti-inflammatories, an additional bioactive agent selected from the group consisting of additional lymphokines or cytokines, and fusion proteins of the lymphokines or cytokines, anti-inflammatories, anti-bacterial, anti-viral, anti-fungal, anti-parasitic, anti-metabolic, anti-inflammatory, vasoactive, anti-neoplastic, bronchodilating, local anesthetic, immunomodulating, growth promoting and regenerating agents, enzymatic, hormonal agents, neurotransmitters, and cell receptor proteins and ligands.

57. The method of claim 55, wherein the subject is selected from the group consisting of normal subjects and subjects afflicted with a condition associated with a viral, bacterial, fungal, and parasitic microorganism, a congenital and acquired immunodeficiency, and a malignancy.

58. The method of claim 57, wherein the subject is an HIV

seropositive human, and the agent is administered, applied, self-administered, or self-applied in an amount and under conditions which avoid increasing the count of circulating microorganisms .

59. The method of claim 29, wherein the subject is a normal subject or a subject afflicted with a condition associated with a viral, bacterial, fungal, and parasitic microorganism, a congenital or acquire immunodeficiency, or a malignancy.

60. The method of claim 59, wherein the subject is an HIV scropositive human; and the composition is administered, applied, self-administered, or self-applied in an amount and under conditions which substantially avoid increasing the count of circulating microorganisms.

L17 ANSWER 3 OF 36 MEDLINE on STN
2002585768 Document Number: 21777034. PubMed ID: 12295184. Interleukin treatment developed for HIV positive patients.
Anonymous. AIDS Wkly Plus, (1999 Jul 12-19) 5. Journal code: 9889385. Report No.: PIP-143305; POP-00286437. Pub. country: United States. Language: English.

AB A treatment of interleukin II (IL-2) is being developed as an immune stimulant for HIV-positive individuals who have responded to medication, but have not had their immune system recover. **While new antiviral drugs are effective in inhibiting HIV, they have not been shown to restore a patient's damaged immune system. IL-2 therapy will be administered to promote the return of normal helper T cells and boost the number of cytotoxic T cells which can then destroy HIV-infected cells.** Pioneered by researchers at Weill Medical College of Cornell University, New York, the low-dose, nontoxic regimen is being investigated in clinical trials. IL-2 has been used as an immune stimulant for cancer patients for more than 10 years. More recently, HIV-positive individuals have been treated with high doses of IL-2, but experienced severe side effects. IL-2 could therefore only be given for a few days every 2 months. This new regimen is different because it involves **the daily low-dose administration of IL-2. Since it appears to be completely nontoxic, patients can be treated without interrupting their daily lives.**

L17 ANSWER 11 OF 36 MEDLINE on STN
2001284103 Document Number: 99704383. PubMed ID: 11367495. Interleukin-2 clinical trials. Anonymous. Newsline People AIDS Coalit N Y, (1998 Sep) 58. Journal code: 9603145. Pub. country: United States. Language: English.

AB Patient selection criteria are presented for three clinical trials using low-dose Interleukin-2 (IL-2) to reconstitute the immune system in HIV-infected patients. These trials are being conducted by the New York Presbyterian Hospital-Cornell Medical Center. In addition to IL-2 therapy, patients will either continue on their existing anti-HIV treatment or receive other specific drug regimens, depending on the study. IL-2 appears to have few side effects and does not seem to stimulate viral replication. IL-2 may also provide certain benefits to the immune system.

L17 ANSWER 13 OF 36 MEDLINE on STN
2001281818 Document Number: 98703558. PubMed ID: 11365210. A view of the future: Dr. Mark Gilbert of Immunex talks about immune based therapy. Interview by Robert Nielsen. Gilbert M. STEP PERSPECTIVE, (1998 Winter) 98 (1) 15-7. Journal code: 9888939. Pub. country: United States. Language: English.

AB Dr. Mark Gilbert, Medical Director of the biopharmaceutical company Immunex, explains that Highly Active Antiretroviral Therapy (HAART) has provided a foundation to begin addressing the effects of therapy on the immune system. Immunex is focusing on the role that Leukine, a recombinant, yeast-derived GM-CSF, has on both advanced AIDS and the early onset of HIV. A Phase III trial is evaluating whether Leukine can reduce the incidence of opportunistic

infections and death in 300 people with AIDS. Dr. Gilbert discusses the importance of the thymus for T cell development and its effect on immune system functions. Immunex is searching for a method to either maintain or to restore the immune system. Restoring the thymus may restore host immunity; however, very little is known about the thymus. According to Gilbert, the most promising idea for restoring immune function is intermittent low-dose interleukin-2 (IL-2). HIV-positive individuals using HAART therapy should consider talking to a health care provider about immune modulation therapy.

L17 ANSWER 14 OF 36 MEDLINE on STN
2001279202 Document Number: 96700637. PubMed ID: 11362594. About interleukin-2. Anonymous. TREATMENT REVIEW, (1995 May) (no 18) 6. Journal code: 9507417. Pub. country: United States. Language: English.

AB Interleukin 2 (IL-2) is a cytokine that helps boost the body's immune system by causing T4 cells to proliferate, or increase in numbers. IL-2 is an approved drug, but not for treatment of AIDS or HIV -related conditions. IL-2 causes HIV growth, although growth rates appear to eventually slow down. Researchers are experimenting with low-dose IL-2 given by subcutaneous injection to see if the rise in T4 counts will restore the normal immune system function. Three new studies combining IL-2 with two other anti-HIV treatments are taking place at the National Institutes of Health and are accepting subjects. Participants interested in these studies, or studies at other sites around the country, should call the Network at (800) 734-7104 for information.

L17 ANSWER 15 OF 36 MEDLINE on STN
2001279113 Document Number: 96700546. PubMed ID: 11362505. Can immune system "small talk" be broadcast as anti-HIV therapy?. Mascolini M. JOURNAL OF THE INTERNATIONAL ASSOCIATION OF PHYSICIANS IN AIDS CARE, (1995 May) 1 (4) 14-22. Journal code: 9508185. ISSN: 1081-454X. Pub. country: United States. Language: English.

AB Speakers at the First International Symposium on HIV and Cytokines, held on March 15-17 in Reims, presented their views on topics in immunology and treatment of HIV infection with respect to cytokines. The first topic addressed the double-edged sword of the immune system which aids the spread of HIV infection as follows: immunostimulation activates both infected resting T cells and uninfected resting T cells, thus spreading HIV infection from one cell population to the other by means of cytokines. The immune system's response during the first weeks of infection focus on HIV 's control of the cytokine network. An examination of the CD8+ antiviral factor in HIV suppression and its enhancement through the introduction of interleukin-2 (IL-2) is presented. Final topics include the safety of low-dose IL-2 therapy; IL-2 and interleukin-12 as interferon-gamma inducers and the use of gene therapy to stimulate interferon-gamma production; an explanation of why HIV disease progresses rapidly in many infants infected in utero; and an examination of HIV protein Tat as a target for antiretroviral therapy to aid in apoptosis (cell suicide) of infected cells.

L17 ANSWER 17 OF 36 MEDLINE on STN

2001278918 Document Number: 95700334. PubMed ID: 11362310. Clinical progress and transmission perils stressed at second human retroviruses conference. Mascolini M. JOURNAL OF THE INTERNATIONAL ASSOCIATION OF PHYSICIANS IN AIDS CARE, (1995 Mar) 1 (2) 19-29. Journal code: 9508185. ISSN: 1081-454X. Pub. country: United States. Language: English.

AB The Second Human Retroviruses Conference covered many topics, including statistics on the viruses' prevalence in American society and some survey results on sexual behavior. Conference meetings were dominated by discussions on protease inhibitors and current clinical trial data on two inhibitors in particular, 3TC and ZDV. Evidence of a new herpes virus causing Kaposi's sarcoma (KS), and research on anti-KS agents, were discussed, including assessments concerning the struggle between the virus and the immune system, and arguments about using immune-based therapies versus attacking the virus directly. Of particular interest concerning immune-based therapy was the National Institute of Allergy and Infectious Diseases' (NIAID) interleukin -2 trial which is showing impressive results in affecting CD4+ counts, if CD4+ counts are not too low initially. Antiretroviral information centered on two investigations surrounding Parke-Davis' PD121871 and PD144975, which seem to prevent activation of latently-infected cells, and return activated cells to a quiescent state. Other conference topics covered acyclovir survival levels, the new therapies and renewed concerns about cytomegalovirus, planning an overall prophylactic strategy, the slow progress in developing a vaccine, and whether low-dose chemotherapy for lymphoma was as good as the standard dose.

L17 ANSWER 24 OF 36 MEDLINE on STN
1999282587 Document Number: 99282587. PubMed ID: 10353861. Efficacy of low-dose subcutaneous interleukin-2 to treat advanced human immunodeficiency virus type 1 in persons with </=250/microL CD4 T cells and undetectable plasma virus load. Arno A; Ruiz L; Juan M; Jou A; Balague M; Zayat M K; Marfil S; Martinez-Picado J; Martinez M A; Romeu J; Pujol-Borrell R; Lane C; Clotet B. (Retrovirology Laboratory "irsiCaixa" Foundation, Immunology Department, HIV Unit, University Hospital "Germans Trias i Pujol," Barcelona, Spain.. lruiz@ns.hugtip.scs.es) . JOURNAL OF INFECTIOUS DISEASES, (1999 Jul) 180 (1) 56-60. Journal code: 0413675. ISSN: 0022-1899. Pub. country: United States. Language: English.

AB The immunologic efficacy of **low-dose recombinant interleukin-2 (rIL-2) administered subcutaneously (sc) once a day in combination with highly active antiretroviral therapy (HAART) was assessed in a pilot study in patients with advanced human immunodeficiency virus (HIV) disease.** Twenty-five persons with </=250 CD4 cells/microL and plasma HIV-1 RNA levels </=500 copies/mL for >24 weeks were randomly assigned to receive sc rIL-2 (3 x 10(6) IU once a day) with their previous antiretroviral regimen (n=13) or to continue with the same treatment (n=12). The level of CD4 T cells was significantly higher in the IL-2 group at week 24 (105+/-65/microL; P<.05) but not in the control group (30+/-78/microL). Memory T cells initially contributed to the CD4 T cell increase at week 4 (P<.05). Naive T cell increases (99+/-58/microL) in the IL-2 group became statistically significant at week 24 compared with the control group (28+/-27/microL; P<.05). Subcutaneous rIL-2 once a day in combination with HAART was well tolerated and improved immunologic surface markers in patients with advanced HIV infection.

L17 ANSWER 25 OF 36 MEDLINE on STN
1999169175 Document Number: 99169175. PubMed ID: 10068580. A randomized trial of high- versus low-dose subcutaneous interleukin-2 outpatient therapy for early human immunodeficiency virus type 1 infection.
Davey R T Jr; Chaitt D G; Albert J M; Piscitelli S C; Kovacs J A; Walker R E; Falloon J; Polis M A; Metcalf J A; Masur H; Dewar R; Baseler M; Fyfe G; Giedlin M A; Lane H C. (National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD 20892-1880, USA. rdavey@atlas. niaid.nih.gov.) JOURNAL OF INFECTIOUS DISEASES, (1999 Apr) 179 (4) 849-58. Journal code: 0413675. ISSN: 0022-1899. Pub. country: United States. Language: English.

AB Forty-nine outpatients infected with human immunodeficiency virus with baseline CD4 cell counts >/=500/mm3, who were **on stable antiretroviral therapy**, were randomized to receive 5-day cycles of either low-dose (1.5 million IU [MIU] twice a day) or high-dose (7.5 MIU twice a day) subcutaneous (sc) interleukin (IL)-2 every 4 or every 8 weeks. High-dose recipients experienced mean slopes of +116.1 cells/month and +2.7 %/month in CD4 cells and percents, respectively, whereas low-dose recipients displayed mean slopes of +26.7 and +1.3% in the same parameters. At month 6, high-dose recipients achieved a 94.8% increase in mean CD4 cells over baseline compared with a 19.0% increase in low-dose recipients. While high-dose recipients encountered more constitutional side effects, these were generally not dose-limiting. High-dose scIL-2 therapy in outpatients with early HIV-1 infection was well tolerated and induced dramatic, sustained rises in CD4 cells.

L17 ANSWER 26 OF 36 MEDLINE on STN
1999023000 Document Number: 99023000. PubMed ID: 9806053.
Coadministration of zidovudine and interleukin-2 increases absolute CD4 cells in subjects with Walter Reed stage 2 human immunodeficiency virus infection: results of ACTG protocol 042. Bartlett J A; Berend C; Petroni G R; Ottinger J; Tyler D L; Pettinelli C; Weinhold K J. (Department of Medicine, Duke University Medical Center, Durham, North Carolina, 27710, USA.) JOURNAL OF INFECTIOUS DISEASES, (1998 Oct) 178 (4) 1170-3. Journal code: 0413675. ISSN: 0022-1899. Pub. country: United States. Language: English.

AB Interleukin-2 (IL-2) can increase numbers of absolute CD4 cells in persons infected with the human immunodeficiency virus who are receiving antiretroviral therapy. **Twenty-five subjects with > 400/mm3 absolute CD4 cells received zidovudine and low-dose intravenous or subcutaneous IL-2 (< or = 10(6) U/m2).** Absolute CD4 cells increased significantly during IL-2 treatment, and 56% of the subjects achieved a maximal increase of > or = 500 cells/mm3. A dose-response relationship favored increasing IL-2 doses, and subcutaneous delivery offered greater increases than intravenous administration. Fifteen subjects had persistent increases of > or = 100 cells/mm3 6 weeks after IL-2 was discontinued. No changes occurred in delayed-type hypersensitivity or helper T cell responses to recall antigens. Cell-mediated cytotoxicities increased against Daudi cells. IL-2 was well tolerated and only 1 subject required dose reduction. Relatively low-dose IL-2 delivered by subcutaneous or intravenous routes may provide an important complement

to antiretroviral therapy to increase absolute CD4 cells with the potential for less toxicity than with higher IL-2 doses.

L17 ANSWER 29 OF 36 MEDLINE on STN
96413659 Document Number: 96413659. PubMed ID: 8816813. **Rational interleukin 2 therapy for HIV positive individuals: daily low doses enhance immune function without toxicity.** Jacobson E L; Pilaro F; Smith K A. (Department of Medicine, New York Hospital-Cornell Medical Center, NY 10021, USA.) PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1996 Sep 17) 93 (19) 10405-10. Journal code: 7505876. ISSN: 0027-8424. Pub. country: United States. Language: English.

AB When administered in high doses to HIV positive (HIV+) individuals, interleukin 2 (IL-2) causes extreme toxicity and markedly increases plasma HIV levels. Integration of the information from the structure-activity relationships of the IL-2 receptor interaction, the cellular distribution of the different classes of IL-2 receptors, and the pharmacokinetics of IL-2 provides for the rationale that low IL-2 doses should circumvent toxicity. Therefore, to identify a nontoxic, but effective and safe IL-2 treatment regimen that does not stimulate viral replication, **doses of IL-2 from 62,500 to 250,000 IU/m2/day were administered subcutaneously for 6 months to 16 HIV+ individuals with 200-500 CD4+ T cells/mm3.** IL-2 was already detectable in the plasma of most HIV+ individuals even before therapy. Peak plasma IL-2 levels were near saturating for high affinity IL-2 receptors in 10 individuals who received the maximum nontoxic dose, which ranged from 187,500 to 250,000 IU/m2/day. During the 6 months of treatment at this dose range, **plasma levels of proinflammatory cytokines remained undetectable, and plasma HIV RNA levels did not change significantly.** However, **delayed type hypersensitivity responses to common recall antigens were markedly augmented, and there were IL-2 dose-dependent increases in circulating Natural Killer cells, eosinophils, monocytes, and CD4+ T cells.** Expanded clinical trials of low dose IL-2 are now warranted, especially in combination with effective antivirals to test for the prevention of immunodeficiency and the emergence of drug-resistant mutants and for the eradication of residual virions.

L17 ANSWER 30 OF 36 MEDLINE on STN
96027492 Document Number: 96027492. PubMed ID: 7579429. **Prolonged administration of low-dose interleukin-2 in human immunodeficiency virus -associated malignancy results in selective expansion of innate immune effectors without significant clinical toxicity.** Bernstein Z P; Porter M M; Gould M; Lipman B; Bluman E M; Stewart C C; Hewitt R G; Fyfe G; Poiesz B; Caligiuri M A. (Department of Hematologic Oncology, Roswell Park Cancer Institute, Buffalo, NY 14263, USA.) BLOOD, (1995 Nov 1) 86 (9) 3287-94. Journal code: 7603509. ISSN: 0006-4971. Pub. country: United States. Language: English.

AB Ten adult patients with human immunodeficiency virus (HIV)-associated malignancies (five with lymphoma and five with Kaposi's Sarcoma) were treated with a daily

subcutaneous injection of interleukin-2 (IL-2) for 90 consecutive days in a phase I dose-escalation study. Seven patients had absolute CD4 counts below 200/mm3 at the time malignancy was diagnosed. Each lymphoma patient had obtained a complete or partial remission with standard chemotherapy before initiating IL-2. The daily dose of IL-2 did not change during the 90-day course of therapy. **Seventeen courses of IL-2 therapy were completed at doses ranging from 0.4 x 10(6) U/m2/d to 1.2 x 10(6) U/m2/d without significant (grade III) toxicity.** Two of two patients experienced grade III toxicity within 21 days of initiating IL-2 at a dose of 1.4 x 10(6) U/m2/d, but both patients subsequently completed 90 days of therapy at the maximum tolerated dose (MTD) of 1.2 x 10(6) U/m2/d. Although there were no significant increases or decreases in T-cell subsets at any dose level, there was an increase in absolute natural killer (NK) cell number at the three highest doses of IL-2 (mean percent increase 247; 95% confidence interval, 124 to 369) that was statistically significant (Wilcoxon one-sample signed rank test, P = .015). One patient developed an anti-IL-2 antibody titer that correlated with minimal NK cell expansion in vitro and in vivo. An increase in eosinophils was noted during 9 of 17 courses of IL-2 therapy without correlation to IL-2 dose, prior course of IL-2, or NK cell expansion. At the MTD, there was no consistent increase in the plasma HIV RNA level over time. Three of 10 patients had progressive disease while on study. During 50 months of IL-2 therapy, no patient was treated for an opportunistic infection. We conclude that **daily low dose subcutaneous IL-2 can be self-administered safely with good compliance for prolonged periods of time to patients with HIV-associated malignancies, including those with profound immune deficiency. The majority of patients show selective expansion of innate immune effectors, ie, NK cells and/or eosinophils, in the absence of significant clinical toxicity or increased viral burden. These results suggest that low-dose IL-2 therapy should be studied further in phase II clinical trials for evidence of activity against malignancy and opportunistic infection in this patient population.**

L17 ANSWER 34 OF 36 MEDLINE on STN

93147738 Document Number: 93147738. PubMed ID: 8093894. **Prolonged immunostimulatory effect of low-dose polyethylene glycol interleukin 2 in patients with human immunodeficiency virus type 1 infection.** Teppler H; Kaplan G; Smith K A; Montana A L; Meyn P; Cohn Z A. (Laboratory of Cellular Physiology and Immunology, Rockefeller University, New York, New York 10021.) JOURNAL OF EXPERIMENTAL MEDICINE, (1993 Feb 1) 177 (2) 483-92. Journal code: 2985109R. ISSN: 0022-1007. Pub. country: United States. Language: English.

AB 13 patients with human immunodeficiency virus type 1 infection class II-IV, but without opportunistic infection or neoplasm, received 6 micrograms **(3.6 x 10(4) IU) of polyethylene glycol recombinant human interleukin 2 (PEG IL-2)** intradermally twice a week for 4 mo were then followed for an additional 6 mo. Clinical, immunological, and viral parameters were monitored in the patients, **all of whom were taking zidovudine.** The cutaneous administration of PEG IL-2 resulted in an indurated zone resembling a delayed-type hypersensitivity response of 26

+/- 1 mm diameter (676 mm2) at 72-96 h after injection throughout the 4 mo of administration. This dose, which was appreciably lower than in most previous trials, was not associated with local or systemic toxicity. No increase in the viral burden of circulating leukocytes or plasma occurred. A number of immunological functions were stimulated by this course of therapy. All patients demonstrated high levels of lymphokine-activated killer cell activity by cells freshly removed from the circulation and in the absence of in vitro exposure to IL-2. Natural killer cell activity was also enhanced. Limiting dilution analysis revealed an increase in the frequency of IL-2-responsive cells from abnormally low to levels above normal during the course of injections. In a subgroup of four patients with > or = 400 CD4+ T cells/microliter at entry, there was a trend to sustained increases in CD4+ T cell numbers. However, this increase did not reach statistical significance. This subset of patients also exhibited higher proliferative responses to phytohemagglutinin as mitogen. Several of these effects persisted for 3-6 mo after cessation of therapy. In conclusion, **low-dose IL-2 regimens lead to sustained immune enhancement in the absence of toxicity. We suggest pursuit of this approach for further clinical trials both as prophylaxis and therapy.**

L17 ANSWER 35 OF 36 MEDLINE on STN
93132377 Document Number: 93132377. PubMed ID: 8421163. **Efficacy of low doses of the polyethylene glycol derivative of interleukin-2 in modulating the immune response of patients with human immunodeficiency virus type 1 infection. Teppler H; Kaplan G; Smith K; Cameron P; Montana A; Meyn P; Cohn Z. (Laboratory of Cellular Physiology and Immunology, Rockefeller University, New York, New York.) JOURNAL OF INFECTIOUS DISEASES, (1993 Feb) 167 (2) 291-8.** Journal code: 0413675. ISSN: 0022-1899. Pub. country: United States. Language: English.

AB Interleukin-2 (IL-2) is a key cytokine in cellular immunity. Human immunodeficiency virus type 1 (HIV-1)-infected individuals lack IL-2 because of low CD4+ T lymphocyte numbers. In an attempt to enhance cellular immunity, **low-dose recombinant human (rh) IL-2 at 10 micrograms or 180,000 units** or its polyethylene glycol (PEG) derivative at 9 micrograms or 36,000 units was given by intracutaneous injection to 8 HIV-1-infected men for 30 days. **Participants had no evidence of opportunistic infection and received concurrent zidovudine.** IL-2 treatment was nontoxic and elicited a local cellular response resembling classic delayed-type hypersensitivity (DTH) with local interferon-gamma production, even in anergic patients. **Systemic responses included enhanced DTH responses to recall antigens, improved in vitro proliferative responses to mitogen, and enhanced NK cell activity.** Peripheral leukocyte phenotype and virus titers were unchanged. Long-term studies of low-dose IL-2 are warranted to determine whether immunoenhancing effects can be sustained and if they are associated with improved clinical course.

L3 ANSWER 163 OF 167 MEDLINE on STN
1999092558 Document Number: 99092558. PubMed ID: 9875399. **Anti-human immunodeficiency virus drug combination strategies.** Vandamme A M; Van Vaerenbergh K; De Clercq E. (Rega Institute for Medical Research, Katholieke Universiteit Leuven, Belgium.. annemie.vandamme@uz.kuleuven.ac.be) . ANTIVIRAL CHEMISTRY AND

CHEMOTHERAPY, (1998 May) 9 (3) 187-203. Ref: 149. Journal code: 9009212. ISSN: 0956-3202. Pub. country: ENGLAND: United Kingdom. Language: English.

AB It is now generally accepted that mono- and bitherapy for human immunodeficiency virus type 1 (HIV-1) infection are only transiently efficient mainly due to virus drug resistance. To obtain a sustained benefit from antiviral therapy, current guidelines recommend at least triple-drug combinations, or the so-called highly active antiretroviral therapy (HAART). **In some patients, HAART can be problematic, either because it is difficult to remain compliant or because previous suboptimum therapies have limited the choice of drugs.** For compliant drug-naive patients, HAART should be able to offer long-term virus suppression, when changing from first- to second- to third-line HAART at drug failure. **Long-term treatment might ultimately result in multi-drug resistant virus leaving few options for salvage therapy.** HIV drug resistance testing to guide this salvage therapy and the development of new drugs to allow new options will therefore remain priorities in anti-HIV drug research.

L3 ANSWER 162 OF 167 MEDLINE on STN

1999392740 Document Number: 99392740. PubMed ID: 10465071. **Salvage therapy with regimens containing ritonavir and saquinavir in extensively pretreated HIV-infected patients.** Fatkenheuer G; Hoetelmans R M; Hunn N; Schwenk A; Franzen C; Reiser M; Jutte A; Rockstroh J; Diehl V; Salzberger B. (Department of Internal Medicine, University of Koln, Germany.) AIDS, (1999 Aug 20) 13 (12) 1485-9. Journal code: 8710219. ISSN: 0269-9370. Pub. country: ENGLAND: United Kingdom. Language: English.

AB OBJECTIVE: To evaluate the efficacy and toxicity of salvage regimens containing ritonavir and saquinavir in patients failing highly active antiretroviral therapy (HAART), and to correlate outcome with plasma concentrations of protease inhibitors. DESIGN: Prospective, non-randomized interventional study. SUBJECTS AND METHODS: Thirty extensively pretreated HIV -infected patients with virological failure under HAART were treated with ritonavir (400 mg twice daily) and saquinavir (600 mg twice daily) and at least one reverse transcriptase inhibitor. HIV -RNA, CD4 cell counts and plasma concentrations of protease inhibitors were determined, and patients were monitored for toxicity at monthly intervals. RESULTS: Six patients showed complete virological success (HIV-RNA <200 copies/ml at week 12) which was sustained for a median follow-up of 6.3 months. Partial virological response (decrease of HIV-RNA of >1 log10 at week 12) was achieved by a further three patients. Patients with a virological response had significantly higher CD4 cell increases than patients without virological response (mean increase at week 12: 66x10(6) cells/l versus 6x10(6) cells/l; P = 0.01). No clinical events were observed during 6 months of follow-up. Neither the use of a non-nucleoside reverse transcriptase inhibitor (NNRTI) nor the number of newly introduced drugs influenced the virological response. Plasma concentrations of protease inhibitors did not statistically differ between patients with and without success. Toxicity included gastrointestinal disturbances, lipid abnormalities and liver dysfunction. CONCLUSIONS: In extensively pretreated patients, **salvage regimens containing ritonavir and saquinavir had only limited and short-term anti-HIV activity and were associated with substantial toxicity.** Plasma concentrations of saquinavir were not predictive for virological response.

L10 ANSWER 297 OF 299 MEDLINE on STN

1998435811 Document Number: 98435811. PubMed ID: 9764782. Clinical outcome and predictive factors of failure of highly active antiretroviral therapy in antiretroviral-experienced patients in advanced stages of HIV-1 infection. d'Arminio Monforte A; Testa L; Adorni F; Chiesa E; Bini T; Moscatelli G C; Abeli C; Rusconi S; Sollima S; Balotta C; Musicco M; Galli M; Moroni M. (Institute of Infectious and Tropical Diseases, University of Milan, Italy.) AIDS, (1998 Sep 10) 12 (13) 1631-7. Journal code: 8710219. ISSN: 0269-9370. Pub. country: United States. Language: English.

AB OBJECTIVE: To verify the effectiveness of highly active antiretroviral therapy (HAART) and to identify any factors predictive of clinical outcome in a clinical setting. DESIGN: Observational study. METHODS: Treatment failure (i.e., the occurrence of new or recurrent AIDS-defining events, death or any definitive discontinuation) and the course of CD4+ cell counts and HIV RNA copies were evaluated in 250 heavily pretreated HIV-infected patients starting HAART [153 with indinavir (IDV), 55 with ritonavir (RTV), 43 with saquinavir (SQV)]. Univariate and multivariate analyses were performed to identify predictors of worse outcome. RESULTS: During a median follow-up of 8 months, 75 patients (30%) had treatment failure because of the occurrence of an AIDS-defining event or death (n = 24), inefficacy (n = 24), or severe intolerance (n = 27). Twenty new and six recurrent AIDS-defining events, and nine deaths occurred (six out of 20 AIDS-defining events and two out of nine deaths within 1 month of treatment). CD4+ counts were above 200 x 10(6)/l at AIDS diagnosis in only two patients. None of the SQV patients, 12 (7.8%) of the IDV patients, and 15 (27.3%) of the RTV-treated patients were considered non-compliant. The SQV-containing regimens independently correlated with treatment failure (relative risk, 2.46; 95% confidence interval, 1.20-5.03; versus IDV). Low compliance partially determined outcome in RTV-treated patients; both severe immunodepression and AIDS at baseline were predictive of treatment failure. There was a 10-fold increase in CD4+ cell counts in the patients treated with IDV and RTV; the best virological outcome occurred in IDV-treated patients, with 68.4% of patients showing undetectable HIV RNA copies after 6 months. CONCLUSIONS: HAART was effective in 70% of patients; low compliance and previous AIDS diagnosis represented predictive factors of therapy failure.

L12 ANSWER 7 OF 8 MEDLINE on STN

88226456 Document Number: 88226456. PubMed ID: 3131227. Pilot study of recombinant human interleukin 2 for chronic type B hepatitis. Kakumu S; Fuji A; Yoshioka K; Tahara H; Ohtani Y; Hirofuji H; Murase K; Aoi T. (Third Department of Medicine, Nagoya University School of Medicine, Japan.) HEPATOLOGY, (1988 May-Jun) 8 (3) 487-92. Journal code: 8302946. ISSN: 0270-9139. Pub. country: United States. Language: English.

AB Recombinant human interleukin 2 was administered to 10 patients with chronic type B hepatitis as a part of a pilot study to evaluate its antiviral activity. Patients received 1 to 3 x 10(5) units per day of interleukin 2 for 21 to 28 days, and all completed the treatment schedule. During therapy, serum values of DNA polymerase decreased in 6 and became negative in four patients. However, when therapy was discontinued, DNA polymerase levels increased to pretreatment levels in most cases. Serum HBeAg levels did not change during treatment. Serum aminotransferase levels transiently increased in 6 of the 10 patients during therapy; but once therapy was stopped, levels fell markedly. Side effects of interleukin 2 therapy included fever, chills, anorexia and fatigue. After 1 year of follow-up, three treated patients had lost HBeAg and had marked improvement in aminotransferase levels. These serologic and biochemical

improvements occurred 1.5 to 11 months after therapy was stopped. Whether a 3- to 4-week course of interleukin 2 therapy leads to an increased rate of seroconversion from HBeAg to antibody in chronic type B hepatitis deserves further evaluation in prospectively randomized, controlled trials.

L14 ANSWER 3 OF 6 MEDLINE on STN
88112994 Document Number: 88112994. PubMed ID: 3501387. Effect of recombinant interleukin 2 on hepatitis B e antigen positive chronic hepatitis. Onji M; Kondoh H; Horiike N; Yamaguchi S; Ogawa Y; Kumon I; Ohta Y. (Third Department of Internal Medicine, Ehime University School of Medicine, Japan.) GUT, (1987 Dec) 28 (12) 1648-52. Journal code: 2985108R. ISSN: 0017-5749. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Eleven patients with hepatitis B (HB) virus related chronic hepatitis were treated with **recombinant interleukin 2 (rIL 2). Two hundred and fifty to 1000 units were given intravenously once daily for seven to 28 days.** In five patients serum glutamic pyruvic transaminase activity rose transiently. Six patients showed a decrease in HBV DNA polymerase. One patient lost HBs, e antigens (Ags) and gained anti-HBs, e antibodies, while one lost HBs Ag and another HBe Ag. 2'-5' oligoadenylate synthetase activity in mononuclear cells in the peripheral blood did not change during treatment. The number of CD4 positive (helper/inducer) cells and natural killer cell activity increased after therapy (p less than 0.05, p less than 0.01). These results suggest that **rIL 2 acts as an immunomodulatory agent enhancing host immune activity and may be beneficial in patients with chronic HB virus infection.**

L16 ANSWER 2 OF 9 MEDLINE on STN
94132539 Document Number: 94132539. PubMed ID: 8301059. Pilot study of natural human interleukin-2 in patients with chronic hepatitis B. Immunomodulatory and antiviral effects. Tilg H; Vogel W; Tratkiewicz J; Aulitzky W E; Herold M; Gruber M; Geissler D; Umlauft F; Judmaier G; Schwulera U; +. (Department of Internal Medicine, Innsbruck University, Austria.) JOURNAL OF HEPATOLOGY, (1993 Sep) 19 (2) 259-67. Journal code: 8503886. ISSN: 0168-8278. Pub. country: Ireland. Language: English.

AB **Ten patients with chronic hepatitis B received increasing doses of nIL-2 (30,000 U, 100,000 U, 300,000 U, 1.0 million U) subcutaneously in a phase I trial.** Each dose was applied once per week over 3 weeks. Serum samples were taken before and 2, 12, 24, 48 and 72 h after the first application of each dose level. Serum concentrations of interleukin-1 (IL-1), IL-2, IL-6, interferon-alfa (IFN-alpha), IFN-gamma, tumor necrosis factor-alpha (TNF-alpha) and GM-CSF as well as the cytokine-dependent serum components neopterin, beta-2-microglobulin (B2M), C-reactive protein (CPR), soluble IL-2-receptor (sIL-2R) and 2'-5'-oligoadenylate synthetase (2-5 OA) were assayed using ELISAs and RIAs. None of the samples tested contained measurable cytokine levels other than IL-2. **A low and non-toxic dose of 300,000 U nIL-2 was already biologically active with induction of neopterin, B2M and sIL-2R.** Dose-dependent changes peaked 24-48 h after application. The same patients were then enrolled in a phase II trial. Treatment in five of the patients was continued twice per week for 3 months with a biologically active dose of 300,000 U nIL-2 subcutaneously. Two of these patients as well as another five patients from the original group were treated with 1.0 million U nIL-2 subcutaneously, twice weekly for 3 months. Neither a biologically active but non-toxic dose of 300,000 U nIL-2, nor a toxic dose of 1.0 million U resulted in permanent clearance of hepatitis B early antigen (HBeAg).(ABSTRACT TRUNCATED AT 250 WORDS)

L19 ANSWER 5 OF 8 MEDLINE on STN
2000190262 Document Number: 20190262. PubMed ID: 10726063. Coinfection by hepatitis B virus and hepatitis C virus. Pontisso P; Gerotto M; Benvegnu L; Chemello L; Alberti A. (Department of Clinical and Experimental Medicine, University of Padova, Italy.. patrizia@ux1.unipd.it) . ANTIVIRAL THERAPY, (1998) 3 (Suppl 3) 137-42. Ref: 43. Journal code: 9815705. ISSN: 1359-6535. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Coinfection by hepatotropic viruses can occur due to the fact that hepatitis B virus (HBV) and hepatitis C virus (HCV) share similar routes of transmission. Different clinical features of liver disease can be observed in infected patients, ranging from fulminant, acute and chronic hepatitis to hepatocellular carcinoma (HCC). The relative role of the infecting viruses in determining the final clinical picture is not yet well defined. Several reports indicate that clinical and pathological severity of liver disease among coinfected patients is increased and in patients with HCC, co-occurrence of both viruses is a common event. The potential mechanism of tumour development still remains speculative, although direct and indirect roles for both HBV and HCV have been proposed. At the molecular level, reciprocal interference of virus replication has been repeatedly described and the extent of interference is influenced by the infecting HCV genotype, genotype 1 of HCV having more efficient inhibitory activity on HBV than genotype 2. Sequence similarities between an arginine-rich nucleocapsid motif of both viruses could support these clinical observations. Concerning response rates to interferon therapy, no satisfactory results have been achieved to date, although identification of effective therapeutic schemes, based on virological status of both viruses are warranted.

L22 ANSWER 4 OF 4 MEDLINE on STN
95269911 Document Number: 95269911. PubMed ID: 7750674. Variants of hepatitis B, C and D viruses: molecular biology and clinical significance. Blum H E. (Department of Internal Medicine, University Hospital Zurich, Switzerland.) DIGESTION, (1995) 56 (2) 85-95. Ref: 125. Journal code: 0150472. ISSN: 0012-2823. Pub. country: Switzerland. Language: English.

AB Variants of hepatitis B virus (HBV), hepatitis C virus (HCV) and of the hepatitis Delta virus (HDV) have been identified in patients both with acute and chronic infections. In the HBV DNA genome, naturally occurring mutations have been found in all viral genes, most notably in the genes coding for the structural envelope and nucleocapsid proteins. In the HCV RNA genome, the regions coding for the structural envelope proteins 1 and 2 as well as the 3'-contiguous nonstructural region 1 were found to be hypervariable. Viral variants may be associated with a specific clinical course of the infection, e.g. acute-fulminant or chronic hepatitis. Specific mutations may reduce viral clearance by immune mechanisms ('immune escape') or response to antiviral therapy ('therapy escape'). Furthermore, mutations of envelope epitopes can lead to viral variants which are not recognized or neutralized by antibodies to wild-type virus, resulting in 'diagnosis escape' or 'vaccine escape'. The exact contribution, however, of specific mutations to the pathogenesis and natural course of HBV, HCV or HDV infection, including the development of hepatocellular carcinoma, remains to be established.

L27 ANSWER 5 OF 9 MEDLINE on STN
1998071233 Document Number: 98071233. PubMed ID: 9407342. T cell

mechanisms in the immunopathogenesis of viral hepatitis B and C.
Tsai S L; Huang S N. (Liver Research Unit, Chang Gung Memorial Hospital and Medical College, Taipei, Taiwan.) JOURNAL OF GASTROENTEROLOGY AND HEPATOLOGY, (1997 Oct) 12 (9-10) S227-35. Ref: 92. Journal code: 8607909. ISSN: 0815-9319. Pub. country: Australia. Language: English.

AB Considerable evidence suggests that immune mechanisms are involved in the pathogenesis of both hepatitis B and C. Both CD4+ and CD8+ T cell responses to viral antigens are important mechanisms that may be responsible for the hepatocyte damage in hepatitis B and C. CD4+ T cell proliferative responses to hepatitis B core antigen (HBcAg) in terms of stimulation index are correlated with hepatitis activity. These responses can be demonstrated in both adult and paediatric patients, and are more vigorous in patients with acute self-limited hepatitis B than in patients with chronic hepatitis B. Patients with hepatitis C also had a significant CD4+ T cell response to hepatitis C virus (HCV) antigens. These responses are also vigorous in acute hepatitis C with recovery than in those cases that evolve to chronic hepatitis C. In terms of human leucocyte antigen (HLA) class I-restricted, CD8+ cytotoxic T lymphocyte (CTL) response, antigenic peptides derived from HBcAg, hepatitis B surface antigen (HBsAg), and polymerase have been demonstrated as the targets for CTL recognition in hepatitis B patients. Multiple CTL epitopes within both HBsAg and HBcAg can be detected by sensitizing target cells with synthetic peptides. Similar to hepatitis B virus (HBV) infection, multispecific, HCV-specific CTL responses can coexist with an extensive quasispecies of viral variants. The mechanisms of viral persistence in both hepatitis B and C are not yet clarified.